ORIGINAL RESEARCH

# Evaluating the Real-World Representativeness of Participants with Mild Cognitive Impairment in Canadian Research Protocols: a Comparison of the Characteristics of a Memory Clinic Patients and Research Samples

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## ABSTRACT

### Background

Studies of mild cognitive impairment (MCI) employ rigorous eligibility criteria, resulting in sampling that may not be representative of the broader clinical population.

### Objective

To compare the characteristics of MCI patients in a Calgary memory clinic to those of MCI participants in published Canadian studies.

### Methods

Clinic participants included 555 MCI patients from the PROspective Registry of Persons with Memory SyMPToms (PROMPT) registry in Calgary. Research participants included 4,981 individuals with MCI pooled from a systematic literature review of 112 original, English-language peer-reviewed Canadian studies. Both samples were compared on baseline sociodemographic variables, medical and psychiatric comorbidities, and cognitive performance for MCI due to Alzheimer's disease and Parkinson's disease.

### Results

Overall, clinic patients tended to be younger, more often male, and more educated than research participants. Psychiatric disorders, traumatic brain injury, and sensory impairment were commonplace in PROMPT (up to 83% affected) but > 80% studies in the systematic review excluded these conditions. PROMPT patients also performed worse on global cognition measures than did research participants.

### Conclusion

Stringent eligibility criteria in Canadian research studies excluded a considerable subset of MCI patients with comorbid medical or psychiatric conditions. This exclusion may contribute to differences in cognitive performance and outcomes compared to real-world clinical samples.

**Key words:** mild cognitive impairment, exclusion criteria, generalizability

## INTRODUCTION

The field of dementia research is focused increasingly on an early phase conceptualized as mild cognitive impairment (MCI).[1] MCI research has significantly advanced the diagnosis, prognosis, and prevention for this condition; however, translating results of this research to practice remains a challenge. Despite the value of past research, MCI participant pools meet rigorous inclusion and exclusion criteria designed to minimize potential confounders and diagnostic errors, resulting in biased case identification[2] and sampling that is not representative of the broader clinical population. Researchers in many fields[2-6] have begun to acknowledge this misalignment between individuals enrolled in research protocols and those with the condition of interest in real-world samples. The representativeness of MCI research and clinic samples has not been quantified in a Canadian context. Given that medical[7] and psychiatric disorders[8] are common in older Canadians and associated with dementia-related outcomes,[9-11] it is important to understand how excluding these

cases from MCI research samples could impact findings and the ability to generalize them to clinical practice in a Canadian context. Such exclusion seems particularly relevant as a growing proportion of cases seen in Canadian memory clinics (for example, in Calgary[12]) have MCI, relative to dementia, which was more common in earlier decades.[13]

This study compared the characteristics of MCI patients in a Calgary memory clinic to those of MCI participants in published Canadian studies. We focused primarily on a clinical, rather than population-based, sample because we were interested in how the representativeness of research cohorts may impact generalizability to clinical practice. We acknowledge that clinical samples may not resemble the broader population in terms of disease severity and prognosis.[14] Given findings from other literature,[2-6] it was hypothesized that memory clinic patients would be more racially diverse, have fewer years of education, more medical and psychiatric comorbidities, and lower scores on baseline cognitive measures, relative to those enrolled in research studies.

## METHODS

Data were drawn from two sources: clinic participants from the PROspective Registry of Persons with Memory SyMPToms (PROMPT) registry[15] in Calgary, and research participants derived from a literature review of Canadian MCI cohorts. The PROMPT registry was selected as convenience sample due to data availability and accessibility. Variables of interest included sociodemographic data (age, sex, education, race), medical issues (cardiovascular/cerebrovascular disease, traumatic brain injury [TBI], vascular risk factors, neurological disorders, sensory impairment, neurological signs), psychiatric comorbidities (mood, anxiety, psychotic and substance abuse disorders, as well as current depressive symptoms) and cognitive performance (Mini-Mental State Examination [MMSE][16] and Montreal Cognitive Assessment [MoCA][17]).

### Patient Population

The PROMPT registry[15] comprises patients from the University of Calgary Cognitive Neurosciences Clinic that offers consultation, assessment, and follow-up services to referred patients with suspected cognitive impairment. All referred patients are eligible for inclusion in the registry with > 90% consenting to enrolment, making it highly representative of the clientele served. In this study, we only included patients initially diagnosed with MCI per the National Institute on Aging and the Alzheimer's Association (NIA-AA) core criteria[18] including: 1) cognitive concern; 2) impairment in ≥ 1 cognitive domain; 3) preserved function; and 4) no dementia. Suspected etiologies were determined based on published reports and criteria,[19-21] pre-existing diagnosis,[22] neuroimaging evidence,[23] and the presence of any core or suggestive features of the etiologies based on psychiatric and physical assessments. MCI was considered due to Alzheimer's disease (MCI-AD) if memory was primarily affected with longitudinal evidence of decline and no major vascular, traumatic or other medical causes.[18] The etiology was considered due to Parkinson's disease (MCI-PD) when there was a pre-existing diagnosis of PD, and to vascular cognitive impairment (MCI-VCI) when there was neuroimaging[23] evidence of vascular insult or history of stroke that was felt sufficient to account for the cognitive issues (this was consistent with criteria from the American Heart Association/American Stroke Association criteria).[23] Other suspected etiologies of MCI included frontotemporal lobar degeneration,[19] Lewy body disease,[20] corticobasal degeneration,[21] and progressive supranuclear palsy.[22]

Sociodemographic information and physician-diagnosed disorders were obtained from patient, informant, and medical records. The 15-item Geriatric Depression Scale (GDS-15)[24] assessed current depressive symptoms. The MMSE[16] and MoCA[17] assessed general cognition.

### Research Participant Population

The systematic review was conducted in accordance with PRISMA guidelines.[25,26] Medline, PsychINFO, EMBASE, and PubMed were searched for studies published prior to July 2018 using the terms: (MCI OR "mild cognitive impairment") AND (Canada[Affiliation/Location]). Inclusion criteria were: 1) English-language; 2) original peer-reviewed research; 3) participants exclusively recruited within Canada; 4) MCI diagnosed using formal criteria (e.g., Petersen's[27] or NIA-AA[18]); and 5) results contained extractable MMSE and/or MoCA scores. When several studies reported on the same dataset, only the largest sample was retained to ensure sample independence. Case studies and multinational studies merging Canadian and non-Canadian data were excluded. Baseline data were used for studies with multiple time points. Four independent reviewers assessed titles, abstracts, and full texts (on selected articles) for eligibility. Two independent reviewers extracted study and sample characteristics. A third independent reviewer resolved any discrepancies.

### Statistics

Descriptive statistics were computed on baseline characteristics of PROMPT patients. Cases with missing data were excluded pairwise from analyses, and no attempt was made to impute data. Cohen's kappa (κ) assessed interreviewer agreement in the systematic review. Descriptive statistics were generated from the weighted mean and standard deviation of age, education, MMSE, and MoCA scores ( Appendix A).

To compare clinic and research samples, chi-square tests with Yates correction and independent samples *t*-tests using weighted means were conducted. Given the most studied suspected etiologies of MCI in the literature were AD or PD (see Results), only these cases were retained from PROMPT and used in comparative analyses. All tests were two-tailed, $\alpha = 0.05$, and 95% confidence intervals were used to determine statistical significance of differences found between samples. The University of Calgary's Conjoint Health Research Ethics Board approved the study (REB18-1007).

## RESULTS

### MCI Clinic Patients

A total of 555 PROMPT patients were diagnosed with MCI (mean age = 65.2, SD = 10.2; mean education = 13.49, SD = 3.41; 56.2% male). As demonstrated in Table 1, there was substantial heterogeneity in the suspected etiologies for MCI found among PROMPT patients. Physical and psychiatric comorbidities, sensory impairment, and traumatic brain injury were common, and 83% of the overall sample had at least 1 of these conditions.

### MCI Research Participants

The literature search resulted in 1,122 potentially relevant articles. After removing duplicates, applying inclusion criteria, and ensuring independence of samples, a total of 112 studies were retained with a total of 4,981 participants (Figure 1). Cohen's κ coefficients were 0.76 (95% CI [0.71, 0.80]) for the title and abstract review stage, and 0.71 (95% CI [0.62, 0.80]) for the full-text review stage, indicating moderate reviewer agreement.

All study characteristics are reported in Appendix B . The retained research studies included 102 observational studies, 6 randomized controlled trials (RCT), 2 non-randomized feasibility studies, 1 randomized feasibility study, and 1 retrospective chart review. Fourteen studies[28-41] (12.5%) did not mention any inclusion/exclusion criteria and five[42-46] (4.5%) had criteria that were not specific to medical or psychiatric conditions. The remaining 93 (83.9%) explicitly excluded select medical, psychiatric, or neurological conditions. Depression and alcohol/substance use concerns were the most frequent exclusionary conditions in 17.0% and 38.4% of published studies, respectively; an additional 25.0% of studies did not specify the psychiatric conditions that were exclusionary. All but one study[44] focused on MCI-AD (N = 4,881) or MCI-PD (N = 100), thus comparisons with PROMPT patients only refer to these MCI subtypes. One study[44] (N = 20) included MCI-VCI, but no comparison analyses were conducted due to the small sample size.

### Clinic vs. Research Participants with MCI-AD and MCI-PD

MCI-AD was diagnosed in 148 PROMPT cases (26.7%), while MCI-PD was diagnosed in 12 (2.2%). Missing data in these cases ranged from 0.7–35.8% for MCI-AD cases (data were primarily missing for current [35.8%] or past [33.8%] history of alcohol abuse, and GDS-15 score [24.8%]), and 18.2–54.5% for MCI-PD cases (mostly missing for current [54.5%] or past [54.5%] history of alcohol abuse, education [27.3%], and GDS-15, MMSE, and MoCA scores [each 18.2%]). Data were missing at random (Little's missing completely at random test: $\chi^2_{(151)} = 169.98$, $p = .14$; $\chi^2_{(31)} = 24.02$, $p = .81$ for MCI-AD and MCI-PD, respectively).

MCI-AD clinic patients were younger, more often male, and more educated than research participants (Table 2). Dyslipidemia and other medical conditions (e.g., cancer, osteoporosis) were more common among clinic than research participants, except for hypertension which was more prevalent among research participants. TBI, psychiatric disorders, and sensory impairment were either not reported or explicitly excluded from all research studies. At least one of these conditions was present in 66.2% of MCI-AD clinic patients. The samples also differed on MMSE and MoCA scores, with clinic patients performing worse on both tests. Further, Cohen's effect size values (*d/h* ranges from 0.22 to 1.27) suggested a small to large practical significance for the aforementioned differences found between clinic patients and research participants.

MCI-PD clinic patients were more educated than research participants, but not different on age or sex (Table 3). TBI, psychiatric disorders, and sensory impairment were again absent from all research studies, and at least one of these conditions was present in 83.3% of MCI-PD clinic patients. Clinic patients also had marginally lower MoCA scores but similar MMSE scores. Further, Cohen's effect size values (*d/h* ranges from 0.53 to 1.77) suggested a moderate to large practical significance for the aforementioned differences found between clinic patients and research participants.

## DISCUSSION

Results from this study indicate that Canadian research participants are not fully representative of MCI patients seen at a local memory clinic, with significant sociodemographic and clinical differences between samples that co-occur with differences in cognitive performance.

Contrary to a priori hypotheses and past findings,[2,4,5] clinic patients were more educated than research participants. It is possible that Quebecois participants, who comprised the majority of published samples, obtained lower total years of schooling despite comparable educational level attained due to province-specific differences[47] (e.g., high school is complete after 11 years in Quebec but 12–13 years elsewhere in Canada). These findings may also be attributed to higher average educational attainment in Calgary as a major site of migration due to job prospects in certain industries (e.g., oil and gas and health care) compared to other major Canadian cities,[48,49] or may reflect cohort differences and secular trends towards higher education in younger generations. Moreover, research studies with a cognitive assessment component may need to make a concerted effort to include individuals with diverse educational backgrounds to avoid ceiling effects as the general population becomes more educated. Regarding sex, there were more men among clinic patients than among research participants. This result is consistent with unbalanced sex distributions in research studies, in which females are typically overrepresented.[50] The potential sex (and, perhaps, gender) differences related to MCI are not fully known. Given mixed results with respect to sex differences in the prevalence and prognosis of MCI,[51-55] future research should aim to systematically examine possible vulnerabilities in older men and women.

In both samples, most individuals were Caucasian. Racial and ethnic minority status has previously been shown to

TABLE 1.
Sociodemographic and health characteristics of MCI cases in the PROMPT registry by etiology

| | *MCI-AD* *n = 148 (26.7% of total)* | *MCI-PD* *n = 12 (2.2%)* | *MCI-FTLD* *n = 44 (7.9%)* | *MCI-DLB* *n = 12 (2.2%)* | *MCI-VCI* *n = 121 (21.8%)* | *MCI-CAA* *n = 7 (1.3%)* | *MCI- DEP* *n = 126 (22.7%)* | *MCI-MD* *n = 39 (7.0%)* | *MCI-PSY* *n =56 (10.1%)* | *MCI-CBGD* *n = 8 (1.4%)* | *MCI-PSP* *n = 6 (1.1%)* | *MCI-Other* *n = 56 (10.1%)* | *MCI-UNSP* *n = 152 (27.4%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, years | 68.61 (9.47) | 66.94 (6.28) | 64.03 (9.01) | 63.10 (5.75) | 68.20 (8.96) | 73.86 (5.97) | 62.29 (6.77) | 72.31 (8.15) | 61.41 (7.47) | 64.52 (5.06) | 67.60 (7.56) | 62.90 (7.30) | 65.62 (8.03) |
| Sex, n (%) | | | | | | | | | | | | | |
| Female | 60 (40.5%) | 2 (16.7%) | 17 (39.5%) | 3 (25.0%) | 48 (40.3%) | 3 (42.9%) | 63 (50.8%) | 11 (28.9%) | 30 (53.6%) | 4 (50.0%) | 4 (66.7%) | 26 (46.4%) | 67 (44.4%) |
| Male | 87 (59.2%) | 10 (83.3%) | 26 (60.5%) | 9 (75.0%) | 71 (59.7%) | 4 (57.1%) | 61 (49.2%) | 27 (71.1%) | 26 (46.4%) | 4 (50.0%) | 2 (33.3%) | 30 (53.6%) | 84 (55.6%) |
| Missing | 1 (0.7%) | | 1 (2.3%) | | 2 (1.7%) | | 2 (1.6%) | 1 (2.6%) | | | | | 1 (0.7%) |
| Education, years | 13.74 (3.97) | 17.67 (4.23) | 13.78 (3.12) | 12.80 (2.36) | 12.63 (2.19) | 11.86 (2.16) | 13.43 (2.60) | 11.68 (2.32) | 12.55 (1.75) | 12.86 (2.12) | 12.40 (7.28) | 13.77 (2.38) | 13.07 (2.36) |
| Race, n (%) | | | | | | | | | | | | | |
| Caucasian | 132 (89.2%) | 9 (75.0%) | 42 (95.5%) | 9 (75.0%) | 114 (94.2%) | 7 (100.0%) | 112 (88.9%) | 33 (86.8%) | 52 (94.5%) | 8 (100.0%) | 5 (83.3%%) | 53 (96.4%) | 134 (88.2%) |
| Non-Caucasian | 15 (10.1%) | 1 (8.3%) | 1 (2.3%) | 3 (25.0%) | 6 (5.0%) | 0 (0.0%) | 12 (9.5%) | 5 (13.2%) | 3 (5.5%) | 0 (0.0%) | 0 (0.0%) | 2 (3.6%) | 14 (9.2%) |
| Missing | 1 (0.7%) | 2 (16.7%) | 1 (2.3%) | | 1 (0.8%) | | 1 (1.6%) | 1 (2.6%) | 1 (1.8%) | | 1 (16.7%) | 1 (1.8%) | 4 (2.6%) |
| Cardiovascular disease, *n* (%) | 29 (19.6%) | 4 (33.3%) | 9 (20.5%) | 3 (25.0%) | 44 (36.4%) | 2 (28.6%) | 28 (22.2%) | 17 (43.6%) | 8 (14.3%) | 1 (12.5%) | 1 (16.7%) | 10 (17.9%) | 40 (26.3%) |
| Coronary artery disease (incl. myocardial infarction) | 17 (11.5%) | 3 (25.0%) | 0 (0.0%) | 2 (16.7%) | 28 (23.1%) | 1 (14.3%) | 14 (11.1%) | 11 (28.2%) | 1 (1.8%) | 0 (0.0%) | 1 (16.7%) | 4 (7.1%) | 20 (13.2%) |
| Atrial fibrillation or flutter | 8 (5.4%) | 0 (0.0%) | 3 (6.8%) | 2 (16.7%) | 7 (5.8%) | 0 (0.0%) | 2 (1.6%) | 5 (12.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 6 (3.9%) |
| Congestive heart failure | 1 (0.7%) | 1 (8.3%) | 1 (2.3%) | 1 (8.3%) | 3 (2.5%) | 0 (0.0%) | 2 (1.6%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) |
| Other | 7 (4.7%) | 0 (0.0%) | 2 (4.5%) | 0 (0.0%) | 9 (7.4%) | 1 (14.3%) | 5 (4.0%) | 3 (7.7%) | 4 (7.1%) | 0 (0.0%) | 0 (0.0%) | 3 (5.4%) | 10 (6.6%) |
| Cerebrovascular disease, *n* (%) | 26 (17.6%) | 2 (16.7%) | 12 (27.3%) | 3 (25.0%) | 45 (37.2%) | 2 (28.6%) | 22 (17.5%) | 12 (30.8%) | 11 (19.6%) | 2 (25.0%) | 0 (0.0%) | 12 (21.4%) | 26 (17.1%) |
| Ischemic stroke | 10 (6.8%) | 1 (8.3%) | 1 (2.3%) | 2 (16.7%) | 16 (13.2%) | 0 (0.0%) | 5 (4.0%) | 6 (15.4%) | 2 (3.6%) | 1 (12.5%) | 0 (0.0%) | 1 (1.8%) | 4 (2.6%) |
| Intracerebral haemorrhage | 2 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 1 (14.3%) | 1 (0.8%) | 0 (0.0%) | 1 (1.8%) | 0 (0.0%) | 0 (0.0%) | 1 (1.8%) | 1 (0.7%) |
| Unspecified stroke | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.8%) | 1 (0.7%) |
| TIA | 9 (6.1%) | 0 (0.0%) | 1 (2.3%) | 0 (0.0%) | 15 (12.4%) | 1 (14.3%) | 9 (7.1%) | 5 (12.8%) | 3 (5.4%) | 0 (0.0%) | 0 (0.0%) | 2 (3.6%) | 7 (4.6%) |
| Other | 5 (3.4%) | 1 (8.3%) | 5 (11.4%) | 1 (8.3%) | 9 (7.4%) | 0 (0.0%) | 2 (1.6%) | 0 (0.0%) | 3 (5.4%) | 0 (0.0%) | 0 (0.0%) | 4 (7.1%) | 7 (4.6%) |
| Traumatic brain injury, *n* (%) | 32 (21.6%) | 2 (16.7%) | 13 (29.5%) | 0 (0.0%) | 26 (21.5%) | 3 (42.9%) | 33 (26.2%) | 8 (20.5%) | 14 (25.0%) | 2 (25.0%) | 1 (16.7%) | 19 (33.9%) | 38 (25.0%) |

TABLE 1. Continued

| | *MCI-AD* *n = 148 (26.7% of total)* | *MCI-PD* *n = 12 (2.2%)* | *MCI-FTLD* *n = 44 (7.9%)* | *MCI-DLB* *n = 12 (2.2%)* | *MCI-VCI* *n = 121 (21.8%)* | *MCI-CAA* *n = 7 (1.3%)* | *MCI- DEP* *n = 126 (22.7%)* | *MCI-MD* *n = 39 (7.0%)* | *MCI-PSY* *n =56 (10.1%)* | *MCI-CBGD* *n = 8 (1.4%)* | *MCI-PSP* *n = 6 (1.1%)* | *MCI-Other* *n = 56 (10.1%)* | *MCI-UNSP* *n = 152 (27.4%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other medical conditions, *n* (%) | 37 (25.0%) | 5 (41.7%) | 28 (63.4%) | 9 (75.0%) | 113 (93.4%) | 4 (57.1%) | 100 (79.4%) | 36 (92.3%) | 47 (83.9%) | 8 (100.0%) | 6 (100.0%) | 43 (76.8%) | 116 (76.3%) |
| Hypertension | 63 (42.6%) | 6 (50.0%) | 15 (34.1%) | 5 (41.7%) | 79 (65.3%) | 3 (42.9%) | 69 (54.8%) | 29 (74.4%) | 25 (44.6%) | 4 (50.0%) | 4 (66.7%) | 18 (32.1%) | 58 (38.2%) |
| Dyslipidemia | 56 (37.8%) | 6 (50.0%) | 12 (27.3%) | 4 (33.3%) | 67 (55.4%) | 2 (28.9%) | 45 (35.7%) | 25 (64.1%) | 17 (30.4%) | 1 (12.5%) | 2 (33.3%) | 14 (25.0%) | 58 (38.2%) |
| Type 2 diabetes | 18 (12.2%) | 1 (8.3%) | 3 (6.8%) | 3 (25.0%) | 30 (24.5%) | 0 (0.0%) | 20 (15.9%) | 10 (25.6%) | 7 (12.5%) | 1 (12.5%) | 0 (0.0%) | 8 (14.3%) | 21 (13.8%) |
| Other[a] | 74 (50.0%) | 2 (16.7%) | 15 (34.1%) | 5 (41.7%) | 66 (54.5%) | 3 (42.9%) | 62 (49.2%) | 24 (61.5%) | 28 (50.0%) | 3 (37.5%) | 5 (83.3%) | 30 (53.6%) | 74 (48.7%) |
| Neurological Disorders, *n* (%) | | 7 (58.3%) | 9 (20.5%) | 8 (66.7%) | 34 (28.1%) | 0 (0.0%) | 25 (19.8%) | 9 (23.1%) | 12 (21.4%) | 6 (75.0%) | 5 (83.3%) | 25 (44.6%) | 35 (23.0%) |
| Parkinsonism | 5 (3.38%) | 3 (25.0%) | 0 (0.0%) | 8 (66.7%) | 8 (6.6%) | 0 (0.0%) | 4 (3.2%) | 4 (10.3%) | 3 (5.4%) | 4 (50.0%) | 4 (66.7%) | 5 (8.9%) | 2 (1.3%) |
| Parkinson's disease | 0 | 3 (25.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (12.5%) | 1 (16.7%) | 0 (0.0%) | 1 (0.7%) |
| Seizures/epilepsy | 4 (2.70%) | 0 (0.0%) | 1 (2.3%) | 0 (0.0%) | 7 (5.8%) | 0 (0.0%) | 3 (2.4%) | 2 (5.1%) | 1 (1.8%) | 0 (0.0%) | 0 (0.0%) | 4 (7.1%) | 4 (2.6%) |
| Delirium | 2 (1.35%) | 0 (0.0%) | 0 (0.0%) | 1 (8.3%) | 4 (3.3%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) |
| Other | 8 (5.41%) | 1 (8.3%) | 4 (9.1%) | 2 (16.7%) | 18 (14.9%) | 0 (0.0%) | 13 (10.3%) | 4 (10.3%) | 4 (7.14%) | 2 (25.0%) | 3 (50.0%) | 14 (25.0%) | 15 (9.9%) |
| Sensory impairment (vision, hearing, unspecified), *n* (%) | 40 (27.0%) | 3 (25.0%) | 19 (43.2%) | 2 (16.7%) | 26 (21.5%) | 0 (0.0%) | 44 (34.9%) | 9 (23.1%) | 16 (28.6%) | 3 (37.5%) | 1 (16.7%) | 12 (21.4%) | 65 (42.8%) |
| Neurological signs, *n* (%) | 61 (41.2%) | 6 (50.0%) | 27 (61.4%) | 9 (75.0%) | 44 (36.4%) | 1 (14.3%) | 54 (42.9%) | 15 (38.5%) | 21 (37.5%) | 8 (100.0%) | 6 (100.0%) | 28 (50.0%) | 70 (46.1%) |
| Gait disorder | 8 (5.4%) | 2 (16.7%) | 0 (0.0%) | 3 (25.0%) | 9 (7.4%) | 0 (0.0%) | 7 (5.6%) | 2 (5.1%) | 2 (3.6%) | 0 (0.0%) | 1 (16.7%) | 3 (5.4%) | 6 (3.9%) |
| Signs of frontal dysfunction | 9 (6.1%) | 0 (0.0%) | 8 (18.2%) | 0 (0.0%) | 5 (5.8%) | 0 (0.0%) | 4 (3.2%) | 4 (10.3%) | 1 (1.8%) | 0 (0.0%) | 1 (16.7%) | 3 (5.4%) | 2 (1.3%) |
| Parkinsonism | 5 (3.4%) | 4 (33.3%) | 1 (2.3%) | 5 (41.7%) | 6 (5.0%) | 0 (0.0%) | 5 (4.0%) | 4 (10.3%) | 2 (3.6%) | 6 (75.0%) | 4 (66.7%) | 6 (10.7%) | 3 (2.0%) |
| Motor neuron signs | 1 (0.7%) | 0 (0.0%) | 1 (2.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Neuro-opthalmologic signs | 2 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 1 (14.3%) | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 1 (1.8%) | 0 (0.0%) |
| Focal or lateralizing signs | 1 (0.7%) | 0 (0.0%) | 1 (2.3%) | 0 (0.0%) | 2 (1.65%) | 1 (14.3%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other | 11 (7.4%) | 0 (0.0%) | 7 (15.9%) | 1 (8.3%) | 10 (8.3%) | 0 (0.0%) | 12 (9.5%) | 3 (7.7%) | 4 (7.1%) | 0 (0.0%) | 0 (0.0%) | 8 (14.3%) | 12 (7.9%) |

TABLE 1. Continued

| | *MCI-AD* *n = 148 (26.7% of total)* | *MCI-PD* *n = 12 (2.2%)* | *MCI-FTLD* *n = 44 (7.9%)* | *MCI-DLB* *n = 12 (2.2%)* | *MCI-VCI* *n = 121 (21.8%)* | *MCI-CAA* *n = 7 (1.3%)* | *MCI- DEP* *n = 126 (22.7%)* | *MCI-MD* *n = 39 (7.0%)* | *MCI-PSY* *n =56 (10.1%)* | *MCI-CBGD* *n = 8 (1.4%)* | *MCI-PSP* *n = 6 (1.1%)* | *MCI-Other* *n = 56 (10.1%)* | *MCI-UNSP* *n = 152 (27.4%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Psychiatric disorders, *n* (%) | 108 (73.0%) | 8 (66.7%) | 27 (61.4%) | 6 (50.0%) | 74 (61.2%) | 2 (28.6%) | 110 (90.9%) | 31 (79.5%) | 45 (80.4%) | 4 (50.0%) | 4 (66.7%) | 34 (60.7%) | 94 (61.8%) |
| Mood disorders | 40 (27.0%) | 6 (50.0%) | 12 (27.3%) | 4 (33.3%) | 42 (34.7%) | 1 (14.3%) | 90 (71.4%) | 13 (33.3%) | 34 (60.7%) | 2 (25.0%) | 2 (33.3%) | 16 (28.6%) | 51 (33.6%) |
| Anxiety disorders | 14 (9.5%) | 1 (8.3%) | 6 (13.6%) | 1 (8.3%) | 14 (11.6%) | 1 (14.3%) | 35 (27.8%) | 6 (15.4%) | 19 (33.9%) | 0 (0.0%) | 0 (0.0%) | 6 (10.7%) | 19 (12.5%) |
| Psychotic disorders | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | 1 (8.3%) | 1 (0.8%) | 0 (0.0%) | 3 (2.4%) | 3 (7.7%) | 2 (3.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) |
| Alcohol and other substance use/ abuse | 25 (16.9%) | 0 (0.0%) | 6 (13.6%) | 5 (41.7%) | 51 (42.1%) | 5 (71.4%) | 27 (21.4%) | 32 (82.1%) | 8 (14.3%) | 0 (0.0%) | 2 (33.3%) | 5 (8.9%) | 2 (1.3%) |
| Other neuropsychiatric symptoms (including PTSD) | 4 (2.7%) | 0 (0.0%) | 1 (2.3%) | 1 (8.3%) | 3 (2.5%) | 0 (0.0%) | 6 (4.8%) | 4 (10.3%) | 2 (3.6%) | 0 (0.0%) | 1 (16.7%) | 2 (3.6%) | 2 (1.3%) |
| GDS-15 | 3.52 (2.96) | 5.33 (3.64) | 3.21 (2.67) | 6.44 (2.17) | 4.11 (2.83) | 1.8 (1.36) | 7 (2.90) | 4.13 (2.91) | 6.10 (3.16) | 6.33 (2.0) | 7.0 (2.4) | 5.29 (2.96) | 3.49 (2.14) |
| Depression severity, *n* (%) | | | | | | | | | | | | | |
| None | 80 (54.1%) | 4 (40.0%) | 30 (78.9%) | 2 (16.7%) | 56 (62.9%) | 4 (57.1%) | 37 (30.1%) | 16 (69.6%) | 17 (35.4%) | 1 (16.7%) | 1 (20.0%) | 25 (46.3%) | 102 (68.0%) |
| Mild | 24 (16.2%) | 4 (40.0%) | 3 (7.9%) | 5 (41.7%) | 22 (24.7%) | 1 (14.3%) | 47 (38.2%) | 4 (17.4%) | 19 (39.6%) | 3 (50.0%) | 1 (20.0%) | 20 (37.0%) | 33 (22.0%) |
| Moderate | 4 (2.7%) | 2 (20.0%) | 3 (7.9%) | 2 (16.7%) | 6 (6.7%) | 0 (0.0%) | 25 (20.3%) | 1 (4.3%) | 7 (14.6%) | 2 (33.3%) | 3 (60.0%) | 7 (13.0%) | 12 (8.0%) |
| Severe | 4 (2.7%) | 0 (0.0%) | 2 (5.3%) | 0 (0.0%) | 5 (5.6%) | 0 (0.0%) | 14 (11.4%) | 2 (8.7%) | 5 (10.4%) | 0 (0.0%) | 0 (0.0%) | 2 (3.7%) | 3 (2.0%) |
| MMSE | 25.79 (3.25) | 27.56 (2.70) | 24.92 (4.22) | 25.18 (2.53) | 26.74 (2.17) | 27.17 (1.17) | 26.99 (2.49) | 25.09 (2.80) | 26.31 (3.41) | 26.75 (1.31) | 25.50 (3.17) | 27.67 (1.86) | 27.43 (1.69) |
| MoCA | 19.90 (3.85) | 24.25 (3.65) | 20.80 (4.02) | 22.22 (4.25) | 21.06 (2.72) | 20.71 (1.55) | 21.97 (2.88) | 19.69 (3.05) | 21.73 (3.63) | 21.50 (2.50) | 20.00 (2.80) | 22.35 (2.94) | 21.98 (3.13) |

*Note*. A proportion of PROMPT clinic patients may have multiple health and/or psychiatric conditions. Therefore, the number of percentages reflects the proportion between the number of participants with the condition and the total sample size for each of the MCI etiology subgroups.

AD = Alzheimer's disease; PD = Parkinson's disease; FTLD = Frontotemporal lobar degeneration; DLB = Dementia with Lewy bodies; VCI = Vascular Cognitive Impairment; CAA = Cerebral amyloid angiopathy; DEP = Depressive symptoms related cognitive impairment; MD = Mixed dementia; PSY = Psychiatric conditions, not including depression; CBGD = Corticobasal ganglionic degeneration; PSP = Progressive supranuclear palsy; Other = Due to systemic, nutritional, or other neurological causes, such as traumatic brain injury, cancer or cancer treatment, etc.; UNSP = Unspecified; PTSD = Post-traumatic stress disorder; TIA = Transient ischemic attack; GDS-15 = 15-Item Geriatric depression scale; MMSE = Mini-mental Status Exam; MoCA = Montreal cognitive assessment

[a]The "Other" category in the other medical conditions includes medical conditions such as hypothyroidism, respiratory disorders, osteoporosis, and medical procedures.

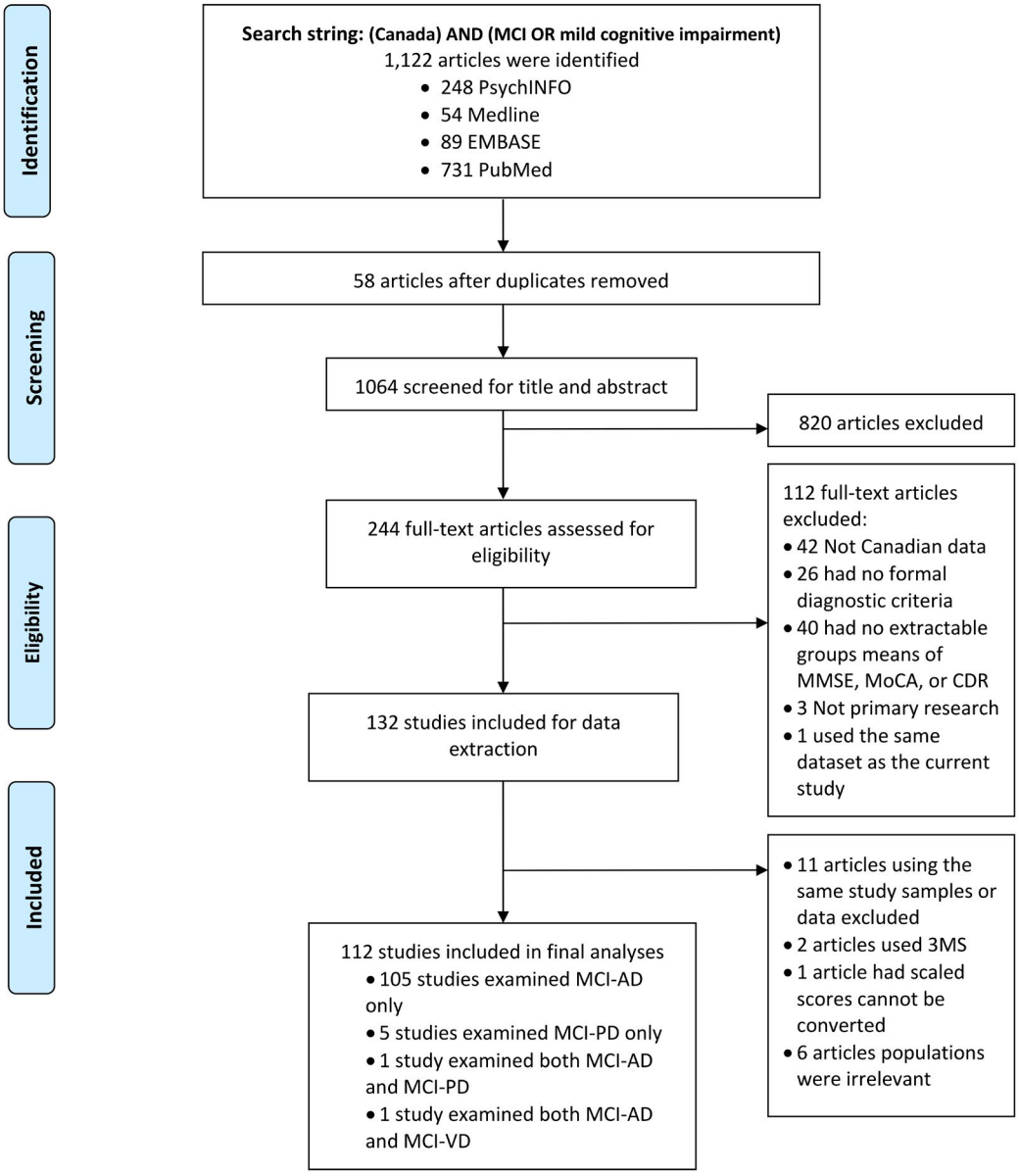


FIGURE 1. Search strategy for the systematic review

be associated with lower health-care literacy,[56] health-care access and utilization,[57] and research participation.[58] The eligibility criteria of language fluency may further limit the number of ethnic minority participants in MCI research studies. Calgary is relatively homogenous, with visible minorities accounting for 33.7% of the population[59] (comparatively, Toronto's population has 51.1% visible minorities[60]). Thus, both samples in this study were less ethnically diverse than anticipated.

Our central finding is that MCI participants with psychiatric, medical, and neurological conditions were regularly excluded from Canadian MCI research studies, despite these conditions being clinically prevalent. Psychiatric disorders, TBI, and sensory impairment were particularly commonplace in PROMPT (83% MCI-PD patients had ≥1), but these conditions were systematic exclusion criteria from > 80% studies in the systematic review. Psychiatric disorders are prevalent among older adults[61-65] and can impact dementia risk and related outcomes.[66-70] The presence of neuropsychiatric symptoms in MCI doubles progression rate to dementia.[71] Cross-sectionally, it is difficult to know whether psychiatric symptoms are a risk factor or a prodrome of dementia.[72] However, large prospective cohorts have demonstrated a linkage between age of onset of psychiatric symptomatology and incident dementia,[73-75] and mild behavioural impairment (MBI, i.e., later life onset of sustained neuropsychiatric symptoms of any severity[76-79]) is an at-risk state for incident cognitive decline and dementia.[80-83] Thus, excluding MCI research participants based on scores above cut-off on a cross-sectional neuropsychiatric measure may inadvertently exclude

TABLE 2.
Sample and health characteristics of MCI-AD participants

| | *PROMPT Registry* | *Systematic Review* | $t/\chi^2$ | *df* | *p* | *95% CI* | *Cohen's d/h* |
|---|---|---|---|---|---|---|---|
| | *n = 148* | *n = 4881* | | | | | |
| *Sociodemographic Characteristics* | | | | | | | |
| Age, years | 68.61 (9.47) | 73.75 (6.98) | **8.67** | **4778** | **< .001** | **[-6.30, -3.97]** | **0.62** |
| Sex, *n* (%) | | | | | | | |
| Female | 60 (40.5%) | 2032(53.7%)[a] | **9.9** | **1** | **0.002** | **[4.97, 20.96]** | **0.26** |
| Male | 87 (59.2%) | 1746 (46.1%) | **9.17** | **1** | **0.002** | **[4.46, 20.50]** | **0.25** |
| Education, years | 13.74 (3.97) | 12.90 (3.61)[b] | **2.53** | **4162** | **0.01** | **[0.19, 1.49]** | **0.22** |
| Race, *n* (%) | | | | | | | |
| Caucasian | 132 (89.2%)[c] | 198 (93.8%)[d] | 0.88 | 1 | 0.35 | [-2.82, 8.85] | 0.15 |
| Non-Caucasian | 15 (10.1%) | 11 (5.2%) | 3.11 | 1 | 0.08 | [-0.59, 11.29] | 0.19 |
| *Health Characteristics* | | | | | | | |
| Cardiovascular disease, *n* (%) | 29 (19.6%) | 46 (26.6%)[e] | 2.18 | 1 | 0.14 | [-2.33, 15.99] | 0.16 |
| Coronary artery disease (incl. myocardial infarction) | 17 (11.5%) | 27 (15.6%) | 1.14 | 1 | 0.29 | [-0.59, 11.29] | 0.12 |
| Atrial fibrillation or flutter | 8 (5.4%) | 9 (5.2%) | 0.01 | 1 | 0.93 | [-3.58, 11.56] | 0.003 |
| Congestive heart failure | 1 (0.7%) | 2 (1.2%) | 0.2 | 1 | 0.66 | [-2.69, 3.49] | 0.05 |
| Other | 7 (4.7%) | 8 (4.6%) | 0 | 1 | 0.96 | [-3.17, 6.08] | 1.06 |
| Cerebrovascular disease, *n* (%) | 26 (17.6%) | 14 (9.9%)[f] | 3.58 | 1 | 0.06 | [-0.33, 15.66] | 0.23 |
| Ischemic stroke/transient ischemic attack | 17 (11.5%) | 14 (9.9%) | 0.19 | 1 | 0.66 | [-5.75, 8.88] | 0.05 |
| Intracerebral haemorrhage | 2 (1.4%) | *n/a* | | | | | |
| Unspecified stroke | 1 (0.7%) | *n/a* | | | | | |
| Other | 5 (3.4%) | *n/a* | | | | | |
| Traumatic brain injury, *n* (%) | 32 (21.6%) | *n/a* | | | | | |
| Other medical conditions, *n* (%) [g] | | | | | | | |
| Hypertension | 63 (42.6%) | 103 (56.3%) | **6.13** | **1** | **0.01** | **[2.87, 24.08]** | **0.28** |
| Dyslipidemia | 56 (37.8%) | 21 (11.5%) | **31.8** | **1** | **<.001** | **[17.17, 35.26]** | **0.63** |
| Type 2 diabetes | 18 (12.2%) | 31 (16.9%) | 1.48 | 1 | 0.22 | [-3.06, 12.26] | 0.14 |
| Other | 74 (50.0%) | 37 (20.2%) | **32.5** | **1** | **<.001** | **[19.57, 37.27]** | **0.64** |
| Neurological Disorders, *n* (%) | 22 (14.86%) | *n/a* | | | | | |
| Parkinsonism | 5 (3.38%) | *n/a* | | | | | |
| Parkinson's disease | 0 | *n/a* | | | | | |
| Seizures/epilepsy | 4 (2.70%) | *n/a* | | | | | |
| Delirium | 2 (1.35%) | *n/a* | | | | | |
| Other | 8 (5.41%) | *n/a* | | | | | |
| Sensory impairment (vision, hearing, unspecified), *n* (%) | 40 (27.0%) | *n/a* | | | | | |
| Neurological signs, *n* (%) | 61 (41.2%) | *n/a* | | | | | |
| Gait disorder | 8 (5.4%) | *n/a* | | | | | |
| Signs of frontal dysfunction | 9 (6.1%) | *n/a* | | | | | |
| Parkinsonism | 5 (3.4%) | *n/a* | | | | | |
| Motor neuron signs | 1 (0.7%) | *n/a* | | | | | |
| Neuro-opthalmologic signs | 2 (1.4%) | *n/a* | | | | | |
| Focal or lateralizing signs | 1 (0.7%) | *n/a* | | | | | |
| Other | 11 (7.4%) | *n/a* | | | | | |
| Psychiatric disorders, *n* (%) | 108 (73.0%) | *n/a* | | | | | |
| Mood disorders | 40 (27.0%) | *n/a* | | | | | |
| Anxiety disorders | 14 (9.5%) | *n/a* | | | | | |
| Psychotic disorders | 1 (0.7%) | *n/a* | | | | | |
| Alcohol and other substance use/abuse | 25 (16.9%) | *n/a* | | | | | |
| Other neuropsychiatric symptoms (including PTSD) | 4 (2.7%) | *n/a* | | | | | |
| GDS-15 | 3.52 (2.96) | 3.47 (2.97) [h] | 0.09 | 150 | 0.92 | [-1.03, 1.13] | 0.02 |

TABLE 2. Continued

| | *PROMPT Registry* | *Systematic Review* | $t/\chi^2$ | *df* | *p* | *95% CI* | *Cohen's d/h* |
|---|---|---|---|---|---|---|---|
| | *n = 148* | *n = 4881* | | | | | |
| Psychiatric disorders, *n* (%) (continued) | | | | | | | |
| Depression severity, *n* (%) | | | | | | | |
| None | 80 (54.1%) | 989 (80.2%) [i] | **40.7** | **1** | **<.001** | **[16.82, 35.50]** | **0.57** |
| Mild | 24 (16.2%) | 245 (19.9%) | 0.87 | 1 | 0.35 | [-4.55, 9.77] | 0.09 |
| Moderate | 4 (2.7%) | 0 (0.0%) | | | | | |
| Severe | 4 (2.7%) | 0 (0.0%) | | | | | |
| *Cognitive Characteristics* | | | | | | | |
| MMSE | 25.79 (3.25) | 27.44 (1.04)[j] | **20.5** | **4344** | **< .001** | **[-1.81, -1.50]** | **0.68** |
| MoCA | 19.90 (3.85) | 23.40 (0.57)[k] | **27.9** | **1255** | **< .001** | **[-3.74, -3.25]** | **1.27** |

*n/a* = Medical, neurological, and psychiatric conditions were either excluded or not reported; Other = medical conditions included conditions such as respiratory disorders, osteoporosis, cancer, and medical procedures.

[a]Twenty articles did not report sex distribution (1096 missing cases).

[b]Thirteen articles did not report years of education information (623 missing cases). Two articles reported education levels in categorical variables (*n* = 226).

[c]One MCI-AD case did not report race/ethnicity information.

[d]Five articles reported race/ethnicity, wherein majority of the samples were Caucasian, with percentages ranging from 67.57% to 100% of the sample (*n* = 211).

[e]Total number of participants with cardiovascular diseases in the literature. Three articles reported participants with cardiovascular diseases (*n* = 173). Percentage reflects the proportion between the number of participants with cardiovascular disease and the total sample size of all the studies reported cardiovascular disease.

[f]Total number of participants with a history of stroke/transient ischemic attack reported in the literature. Two articles reported participants with cerebrovascular diseases (*n* = 141). Percentage reflects the proportion between the number of participants with a history of stroke/transient ischemic attack and the total sample size of all the studies reported cerebrovascular events.

[g]Three studies reported multiple medical conditions (*n* = 183). Subsequent percentage reflects the proportion between the number of participants with the specific medical condition and the total sample size of all studies reported other category of the other medical condition.

[h]Three articles used GDS-15 to report research participants' depressive symptoms (*n* = 40)

[i]Thirty articles used self-report measures to assess depressive symptoms (*n* = 1234), other than the GDS-15. Percentage represents the proportion between the number of participants in each severity category based on established cut-off scores and the total sample size of all the articles with depressive symptoms questionnaires.

[j]Ninety-three articles used MMSE and two articles used standardized MMSE (SMMSE) to assess general cognition (*n* = 4224). Scores of MMSE and SMSSE are comparable.

[k]Thirty articles used MoCA to assess general cognition (*n* = 1150).

those with prodromal disease, diluting the sample. The data on MBI can inform the approach to psychiatric conditions in MCI, and including those with MBI may, in fact, enrich the MCI sample for prodromal dementia.

Sensory impairment is common in late life[84-88] and is associated with increased risk of MCI[89] and dementia,[90-93] especially multisensory impairment.[94] Sensory impairment may even serve as a potential biomarker for pathological cognitive aging.[95] Similarly, TBI is another identified risk factor for MCI[96-98] and dementia,[99,100] and is associated with neurodegenerative protein pathology.[101,102] The presence of chronic, systemic health conditions can also exacerbate cognitive decline.[103-107] Given that chronic health conditions and sensory impairments are highly prevalent among Canadian seniors[7,84,85,108] and older adults are at high risk of sustaining a TBI,[109,110] the exclusion of these comorbidities may further undermine the representativeness of MCI samples and research findings. Predictably, these comorbidities were accompanied by between-sample discrepancies in cognitive performance in this study—clinic patients performed approximately two points lower on MMSE and MoCA testing compared to research participants. The magnitude of study effects is likely to be over- or underestimated in MCI research participants who are overall healthier with less cognitive impairment relative to current real-world patient populations. It is additionally possible that healthier, less cognitive impaired individuals self-select into research protocols, further reducing generalizability. Canadian practitioners seeking to implement evidence-based care should carefully consider the characteristics of relevant research samples before applying results derived from them in their practice.

The search terms used in the systematic review were selected to best match the criteria used to diagnose patients in PROMPT. As such, some important Canadian studies of cognitive impairment, no dementia (CIND) or vascular cognitive impairment (VCI)[111] were not captured, such as the Canadian Study of Health and Aging (CSHA),[112] the Canadian Collaborative Cohort of Related Dementias (ACCORD),[113] and the Consortium to Investigate Vascular Impairment of Cognition (CIVIC).[111] The concepts underlying CIND are considerably different from Petersen's[27] and NIA-AA's[18] conceptualization of MCI, as CIND encompasses non-neurodegenerative and not necessarily progressive causes of cognitive impairment[114] (including psychiatric, neurodevelopmental and toxic).[113] Nonetheless, these studies offer similar insights to the present work. ACCORD[113] and CIVIC[111] were carried

out in Canadian dementia clinics and, like PROMPT, participants frequently had medical and psychiatric comorbidities. CSHA[112] also documented depression (8.0%), psychiatric conditions (6.6%), and substance abuse (8.3%) as common contributors to cognitive decline. Average MMSE scores in ACCORD[113] were similar to those in PROMPT (M = 26.9, SD = 3.0), while those in CIVIC[111] were lower (M = 21.9, SD = 6.2). The differences in the MMSE scores between PROMPT and CIVIC patients may be attributable to the fact that they were a decade older, on average, than PROMPT patients and may have had more severe neurological damage (e.g., stroke).

Our results highlight the diverse presumed neuropathological etiologies of MCI in clinical practice, which is not reflected in the Canadian research literature. The vast majority (95%) of identified published studies focused on MCI due to

TABLE 3.
Sample and health characteristics of MCI-PD participants

| | *PROMPT Registry n = 12* | *Systematic Review[a] n = 100* | *t/χ²* | *df* | *p* | *95% CI* | *Cohen's d/h* |
|---|---|---|---|---|---|---|---|
| *Sociodemographic Characteristics* | | | | | | | |
| Age, years | 66.94 (6.28) | 66.45 (6.87) | 0.24 | 110 | .81 | [-3.64, 4.62] | 0.07 |
| Sex, *n* (%) | | | | | | | |
| Female | 2 (16.7%) | 29 (35.4%)[b] | 1.67 | 1 | .20 | [-10.74, 34.15] | 0.43 |
| Male | 10 (83.3%) | 53 (64.6%) | 1.64 | 1 | .20 | [-10.99, 34.82] | 0.43 |
| Education, years | 17.67 (4.23) | 13.88 (3.49) | **3.07** | **107** | **.003** | **[1.34, 6.24]** | **0.98** |
| Race/Ethnicity, *n* (%) | | | | | | | |
| Caucasian | 9 (90.0%)[c] | 22 (100%)[d] | | | | | |
| Non-Caucasian | 1 (10.0%) | | | | | | |
| *Health Characteristics* | | | | | | | |
| Cardiovascular disease, *n* (%) | 4 (33.3%) | *n/a* | | | | | |
| Coronary artery disease | 3 (25.0%) | *n/a* | | | | | |
| Atrial fibrillation or flutter | 0 (0.0%) | *n/a* | | | | | |
| Congestive heart failure | 1 (8.3%) | *n/a* | | | | | |
| Other | 0 (0.0%) | *n/a* | | | | | |
| Cerebrovascular disease, *n* (%) | 2 (16.7%) | *n/a* | | | | | |
| Ischemic stroke | 1 (8.3%) | *n/a* | | | | | |
| Intracerebral haemorrhage | 0 (0.0%) | *n/a* | | | | | |
| Unspecified stroke | 0 (0.0%) | *n/a* | | | | | |
| Other | 1 (8.3%) | *n/a* | | | | | |
| Traumatic brain injury, *n* (%) | 2 (16.7%) | *n/a* | | | | | |
| Other medical conditions, *n* (%) | | | | | | | |
| Hypertension | 6 (50.0%) | *n/a* | | | | | |
| Dyslipidemia | 6 (50.0%) | *n/a* | | | | | |
| Type 2 diabetes | 1 (8.3%) | *n/a* | | | | | |
| Other[e] | 2 (16.7%) | *n/a* | | | | | |
| Neurological Disorders, *n* (%) | 7 (58.3%) | *n/a* | | | | | |
| Parkinsonism | 3 (25.0%) | *n/a* | | | | | |
| Parkinson's disease | 3 (25.0%) | *n/a* | | | | | |
| Seizures/epilepsy | 0 (0.0%) | *n/a* | | | | | |
| Delirium | 0 (0.0%) | *n/a* | | | | | |
| Other | 1 (8.3%) | *n/a* | | | | | |
| Sensory impairment (vision, hearing, unspecified), *n* (%) | 3 (25.0%) | *n/a* | | | | | |
| Neurological Signs | 6 (50.0%) | *n/a* | | | | | |
| Gait disorder | 2 (16.7%) | *n/a* | | | | | |
| Signs of frontal dysfunction | 0 (0.0%) | *n/a* | | | | | |
| Parkinsonism | 4 (33.3%) | *n/a* | | | | | |
| Motor neuron signs | 0 (0.0%) | *n/a* | | | | | |
| Neuro-opthalmologic signs | 0 (0.0%) | *n/a* | | | | | |
| Focal or lateralizing signs | 0 (0.0%) | *n/a* | | | | | |
| Other | 0 (0.0%) | *n/a* | | | | | |

TABLE 3. Continued

| | *PROMPT Registry n = 12* | *Systematic Review*[a] *n = 100* | $t/\chi^2$ | *df* | *p* | *95% CI* | *Cohen's d/h* |
|---|---|---|---|---|---|---|---|
| Psychiatric disorders, *n* (%) | 8 (66.7%) | *n/a* | | | | | |
| Mood disorders | 6 (50.0%) | *n/a* | | | | | |
| Anxiety disorders | 1 (8.3%) | *n/a* | | | | | |
| Psychotic disorders | 0 (0.0%) | *n/a* | | | | | |
| Alcohol and other substance use/abuse | 0 (0.0%) | *n/a* | | | | | |
| Other neuropsychiatric symptoms (including PTSD) | 0 (0.0%) | *n/a* | | | | | |
| GDS-15 | 5.33 (3.64) | *n/a* | | | | | |
| Depression severity, *n* (%) | | | | | | | |
| None | 4 (40.0%) | 47 (100.0%)[f] | **30.97** | **1** | **<.001** | **[30.29,83.18]** | **1.77** |
| Mild | 4 (40.0%) | 0 (0.0%) | **19.86** | **1** | **<.001** | **[15.62,68.73]** | **1.37** |
| Moderate | 2 (20.0%) | 0 (0.0%) | **9.57** | **1** | **.002** | **[3.80, 50.98]** | **0.93** |
| Severe | 0 (0.0%) | 0 (0.0%) | 0 | 0 | 1 | [0.0, 0.0] | |
| *Cognitive Characteristics* | | | | | | | |
| MMSE | 27.56 (2.70) | 28.07 (1.23)[g] | 0.93 | 50 | .36 | [-1.61, 0.59] | 0.24 |
| MoCA | 24.25 (3.65) | 25.82 (2.02)[h] | **2.06** | **69** | **.04** | **[-3.09, -0.05]** | **0.53** |

*n/a* = Medical, neurological, and psychiatric conditions were either excluded or not reported.
[a]Two studies did not report any inclusion/exclusion criteria or any medical or psychiatric comorbidities. Four studies provided inclusion/exclusion criteria based on current or history of systemic or psychiatric illnesses (see Appendix A).
[b]One article did not report sex distribution (18 missing cases).
[c]Two MCI-PD cases did not report race information.
[d]One article reported race/ethnicity, wherein 100% of sample was Caucasians (*n* = 22).
[e]The "Other" category of other medical conditions included Meniere's disease, arthritis, and hypothyroidism.
[f]Depression severity frequency was determined based on published severity cut-off scores of the average total scores of the Hamilton Depression Rating Scale (HAM-D) or the Beck Depression Inventory-II (BDI-II) found in three articles, *n* = 47.
[g]Two Studies used MMSE to measure general cognition, *n* = 40.
[h]Four articles used MoCA to measure general cognition, n = 60.

AD, conceptualized as cognitive impairment primarily affecting memory not better accounted for by other neurologic insults. In the PROMPT sample, however, only about a quarter of patients were thought to have pure AD as the cause for MCI. Many more cases were presumed to have a vascular etiological basis in whole or in part, as well as a large number of other conditions. These results, together with the broader findings of multiple comorbidities in our clinical sample, support our initial hypothesis that memory clinic patients are considerably more diverse in many respects than those included in research studies.

**Strengths and Limitations**

This study represents an important first step in evaluating the real-word representativeness of participants with MCI in Canadian research protocols, and demonstrates key differences between characteristics of memory clinic patients and research samples. Our clinical MCI cohort was fairly large and diverse, and considered generally representative of the MCI clientele served in Calgary. However, it represented a convenience sample that is likely to differ from other Canadian MCI cohorts, and findings may not be generalizable to clinics in other parts of Canada and elsewhere. Our findings may also not be generalizable to population-based samples of person with MCI. Other limitations include the fact that we only examined cognitive performance on the MMSE and MoCA tests; a more comprehensive neuropsychological battery could provide more information about relevant differences between clinic and research samples. Nevertheless, findings highlight the importance of interpreting MMSE and MoCA scores together with patients' medical and psychiatric history. While we attempted to ensure sample independence in the systematic review, certain participants may have ended up in multiple studies, which could have inflated between-group differences. Moreover, multiple comparison tests may have inflated Type I error rates. Therefore, results should be interpreted with caution; however, substantial effect sizes were found for the aforementioned comparison tests, suggesting practical significance. The accuracy of the etiological diagnoses assigned to the MCI cases in PROMPT cannot be guaranteed, nor can those of patients included in the studies within the systematic review. In PROMPT, routine clinical protocols for determination of presumed etiology did not include AD biomarker testing, which is currently recommended in Canada for research only,[115] or neuropathological confirmation. The prevalence of mixed or multiple etiologies was also likely underestimated. Further, we did not examine differences between sub-types of MCI-AD (amnestic vs. non-amnestic). Given that MCI-PD patients are often seen at movement disorders clinics, patients with this form of MCI

were likely underrepresented in the current study. We were unable to examine the MCI-VCI subpopulation, considering this group was underrepresented in the MCI research studies identified in the literature, despite vascular disease being a common contributor to cognitive impairment. Lastly, findings may not be generalizable to non-Caucasian groups.

Despite these limitations, given its relatively large and diverse clinic sample, the current study serves as an important initial step in demonstrating key demographic and clinical differences among MCI memory clinic patients and research participants in Canada.

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**CONFLICT OF INTEREST DISCLOSURES**

The authors declare that no conflicts of interest exist.

**APPENDICES**

## **Appendix A.** Weighted mean and pooled standard deviation calculation

The weighted mean is a form of average. However, instead of each data point contributing equally to the final average (i.e., an arithmetic mean), some data points contribute more to the final average than others. The weighted mean is calculated by multiplying each data point by the weight, and then dividing it by the sum of all the weights. The weighted mean in the current systematic review was calculated by multiplying the mean scores in each study (i.e., age, years of education, and the MMSE and MoCA scores) by each study's sample size (i.e., the weight). This was then divided by the sum of the sample sizes in all studies. See the weighted mean formula below:

$$\overline{x}_{weighted} = \frac{\sum_{i=1}^{n}(x_i * w_i)}{\sum_{i=1}^{n} w_i}$$

$x$ = mean; $w$ = sample size

The pooled standard deviation is the weighted average of standard deviations. The pooled standard deviation was calculated by: 1) subtracting 1 from each sample size; 2) then multiply the value by the sample variance (i.e., squaring the standard deviation) and sum the multiplied value for all studies; 3) dividing the results from the first two steps by the overall sample size minus the total number of studies; and 4) taking the square root of the weighted variance terms. See the pooled standard deviation formula below:

$$SD_{pooled} = \sqrt{\frac{\sum_{\mathbf{k}=1}(n_k - 1) * SD_k^2}{(\sum n_k) - k}}$$

For studies that reported median, range, or interquartile range, the mean and standard deviations were estimated via an online calculator (http://www.comp.hkbu.edu.hk/~xwan/median2mean.html). Specifically, if the range of a score was provided in an article, the standard deviation of the sample was estimated using methods proposed by Hozo *et al*.[1] If the article presented only median and interquartile range, the mean of the sample was estimated using methods proposed by Luo and colleagues,[2] and the standard deviation was estimated using methods proposed by Wan and colleagues.[3]

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**Appendix B.** Articles retained in the systematic review

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kabani et al.[28] | Québec | 15 | *M* = 77.4, *SD* = 5.8 | F: 8 (53.33%) M: 7 (46.67%) | | | Petersen[116] | *M* = 27.73 | | | Observ. | No mention of exclusion criteria |
| Massoud et al.[117] | Québec | 13 | *M* = 76.5, *SD* = 4.94 | | | *M* = 10.4, *SD* = 3.78 | ICD-10[118] | *M* = 26.5, *SD* = 2.01 | | | Prospect cohort | **Exclusion:** Serious chronic medical illness or cancer, CVD, clinical, laboratory work or neuroimaging data suggestive of another cause for dementia, use of psychoactive drugs, corrected central acuity < 20/50, and inability to perform at least 2 tests/procedures |
| Whatmough et al.[119] | Québec | 16 | *M* = 74.5, *SD* = 9.1 | F: 4 (25%) M: 12 (75%) | | *M* = 13, *SD* = 3.9 | Petersen[120] | *M* = 27.2, *SD* = 1.7 | | | Observ. | **Exclusion:** Blood work confirmed treatable illnesses |
| Berlin et al.[121] | Québec | 106 | *M* = 75.4, *SD* = 6.8 | | | *M* = 11.9, *SD* = 3.8 | Petersen[122] | *M* = 27.9, *SD* = 1.6 | | | Observ. | **Exclusion:** Medical or neurological conditions that explain the cognitive decline |
| Chantal et al.[123] | Québec | 14 | *M* = 69.2, *SD* = 6.8 | F: 5 (35.71%) M: 9 (64.39%) | | *M* = 10.3, *SD* = 4.1 | Petersen[124] | *M* = 27.0, *SD* = 1.4 | | | Observ. | **Exclusion:** Current use of cognitive enhancer, current or past systemic (incl. type 2 diabetes) or psychiatric illness or TBI that may affect cognitive function |
| Phillips et al.[29] | Québec | 16 | *M* = 75.8, *SD* = 6.4 | F: 4 (25%) M: 12 (75%) | | *M* = 10.4, *SD* = 3.6 | Petersen[122] | *M* = 27.6, *SD* = 2.1 | | | Observ. | No mention of exclusion criteria |
| Geslani et al.[125] | Ontario | 57 | *M* = 73.07, *SD* = 7.72 | F: 36 (63.16%) M: 21 (36.84%) | | *M* = 12.67, *SD* = 3.24 | Petersen[122] | *M* =26.58, *SD* = 2.20 | | | Observ. | **Exclusion:** Must be fluent in English, have adequate hearing and vision to complete testing, any neurological condition that may cause memory impairment, DSM-III-R criteria for dementia, evidence of chronic alcohol or other drug abuse, stroke hypoxia, intracranial mass lesions, psychoses, brain trauma |
| Levinoff et al.[126] | Québec | 34 | *M* = 74.1, *SD* = 7.1 | | | *M* = 10.5, *SD* = 3.6 | Petersen[122] | *M* = 27.7, *SD* = 2.1 | | | Observ. | **Exclusion:** Additional neurological disorders that interfere with normal cognitive functioning, structural brain diseases confirmed by CT and/or MRI |
| Belleville et al.[127] | Québec | 28 | *M* = 62.33, *SD* = 7.3 | | | *M* = 14.6, *SD* = 5 | Petersen[128] | *M* =28.94, *SD* = 1.2 | | GDS: *M* = 8.1, *SD* = 3.8 | N-rand feasibil | **Exclusion:** Uncorrected vision or hearing impairment, use of psychotropic medications known to impair cognition, physical mobility or manual dexterity impairment, intellectual deficiency, alcoholism or toxicomania, presence or history of severe psychiatry disorder, cerebrovascular disorders, neurological disorder, general anesthesia in the past 6 months |
| Duong et al.[129] | Québec | 61 | *M* = 74.68, *SD* = 6.48 | | | *M* = 11.03, *SD* = 3.69 | Chertkow et al.[130] | *M* = 27.2, *SD* = 2.25 | | | Observ. | **Exclusion:** Presence of any medical, neurological, or psychiatric explanation for memory loss, except for mild depression |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hudon et al.[131] | Québec | 14 | *M* = 66.6, *SD* = 11.9 | F: 11 (78.57%) M: 3 (21.43%) | | *M* = 13.9, *SD* = 3.6 | Petersen[27] | *M* = 28.1, *SD* = 1.5 | | | Observ. | **Exclusion:** History of TBI, stroke or transitory cerebral ischemia, former intracranial surgery, neurological disorder of cerebral original or associated with another form of dementia, significant psychiatric illness, significant vascular risk factors, alcoholism/drug addiction or excessive alcohol consumption based on DSM-IV, and general anesthesia in the past 12 months |
| Levinoff et al.[34] | Québec | 73 | *M* = 74, *SD* = 7.3 | | | *M* = 12.7, *SD* = 3.4 | Petersen[132] | *M* = 27.7, *SD* = 1.9 | | | Observ. | No mention of exclusion criteria |
| Murphy et al.[133] | Ontario | 33 | *M* = 76.6, *SD* = 5.4 | F: 16 (48.48%) M: 17 (51.52%) | | *M* = 13.9, *SD* = 3.6 | Petersen[27] | *M* = 27.8, *SD* = 1.4 | | | Observ. | **Exclusion:** Medical or psychiatric illness that may contribute to cognitive decline. |
| Singh et al.[35] | Québec | 65 | *M* = 75, *SD* = 6 | F: 34 (52.31%) M: 26 (47.69%) | | | Petersen[128] | *M* = 26.9, *SD* = 2.5 | | | Observ. | No mention of exclusion criteria |
| Belleville et al.[134] | Québec | 25 | *M* = 64.76, *SD* = 10.83 | F: 14 (56%) M: 11 (44%) | | *M* = 14.32, *SD* = 4.71 | Petersen[135] | *M* =28.36, *SD* = 1.98 | | | Observ. | **Exclusion**: Non-amnestic MCI subtypes, alcohol abuse, presence or history of severe psychiatric disorder, intellectual deficiency, GDS scores > 17, CVD, neurological disorder, systemic diseases know to contribute to cognitive impairment, general anesthesia in the last 6 months, significant impairment of hand mobility, and uncorrected hearing and vision |
| Standish et al.[42] | Ontario | 166 | | | | | Petersen[128] | SMMSE: *M* = 27.1, *SD* = 2.30 | | | Cross- sect | **Exclusion:** Participants able to communicate in English, and those with GDS scores > 7 |
| Babins et al.[136] | Québec | 82 | *M* = 74.85, *SD* = 6.04 | | | *M* = 11.2, *SD* = 3.43 | Petersen[122] | *M* =27.21, *SD* = 1.84 | | | Observ. | **Inclusion:** Participants had no evidence of systemic or neurological disease that may affect cognitive function **Exclusion:** Structural brain disease confirmed by computed tomography and/or magnetic resonance imaging |
| Belleville etal.[137] | Québec | 20 | *M* = 66.3, *SD* = 10.9 | F: 12 (60%) M: 8 (40%) | | *M* = 13.9, *SD* = 5 | Petersen[135] | *M* =28.15, *SD* = 2.1 | | | Observ. | **Exclusion:** Non-amnestic MCI, current or a history of alcoholism, severe psychiatric disorder, significant cerebrovascular disorder, neurological disorder, intellectual deficiency, systemic disease known to impair cognition, general anaesthesia in the past 6 months, significant impairment of hand mobility |
| Clément et al.[138] | Québec | 68 | *M* = 69.06, *SD* = 7.89 | | | *M* = 13.88, *SD* = 4.34 | Petersen[122] | *M* =27.96, *SD* = 1.76 | | GDS-5: *M* = 1.09, *SD* = 1.18 | Observ. | **Exclusion:** Presence of any significant systemic, neurological, or psychiatric illnesses that may explain cognitive impairment |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Djordjevic et al.[139] | Québec | 51 | *M* = 75.4, *SD* = 6.75 | F: 26 (50.98%) M: 25 (49.02%) | | *M* = 11.5 | Chertkow et al.[130] | *M* = 27.26 | | GDS: *M* = 6.12 | Observ. | **Exclusion:** Presence of neurological, psychiatric, or other medical factors that may affect olfaction |
| Fellows et al.[140] | Québec | 90 | *M* = 73.7, *SD* = 8.2 | F: 45 (50%) M: 45 (50%) | | *M* = 10.7, *SD* = 3.5 | Petersen [116,122] | *M* = 27.5, *SD* = 1.9 | | | Prospect long | **Exclusion:** Major depression via <16 on the GDS, systemic or other neurological disease that may interfere with cognitive function, structural brain disease |
| Houde et al.[36] | Québec | 60 | *M* = 74.5, *SD* = 6.5 | F: 31 (51.67%) M: 29 (48.33%) | | *M* = 10.5, *SD* = 3.1 | Petersen[128] | *M* = 27.2, *SD* = 1.9 | | GDS: *M* = 10.4, *SD* = 5.7 | Observ. | No mention of exclusion criteria |
| Murphy et al.[141] | Ontario | 17 | *M* = 76.2, *SD* = 5.7 | F: 10 (58.82%) M: 7 (41.18%) | | *M* = 14.5, *SD* = 2.8 | Petersen[27] | *M* = 27.3, *SD* = 2 | | | Observ. | **Exclusion:** Medical or psychiatric conditions that may account for memory decline, other than possible incipient AD (through medical history review and current self-report mood status via the GDS or HADS) |
| Troyer et al.[142] | Ontario | 29 | *M* = 75.1, *SD* = 7 | F: 16 (55.17%) M: 13 (44.83%) | | *M* = 14.3, *SD* = 2.6 | Petersen[27] | *M* = 27.8, *SD* = 1.7 | | | Observ. | **Exclusion:** Medical or psychiatric disease that may account for memory impairment |
| Troyer et al.[143] | Ontario | 68 | *M* = 75.4, *SD* = 6.8 | F: 36 (52.94%) M: 32 (47.06%) | | *M* = 14.5, *SD* = 3.3 | Petersen[27] | *M* = 27.7 1.7, *SD* = | | HADS-Depression: *M* = 9.1, *SD* = 5.9 | Random control trial (RCT) | **Exclusion:** Medical or psychiatric condition that may account for memory impairment |
| Bélanger & Belleville[144] | Québec | 18 | | | | | Petersen[135] | *M* = 27.3, *SD* = 1.8 | | | Observ. | **Exclusion**: Presence of any significant systemic, neurological, or psychiatric condition that may contribute to cognitive impairment |
| Brambati et al.[145] | Québec | 25 | *M* = 73.44, *SD* = 7.05 | F: 17 (68%) M: 8 (22%) | | *M* = 13.21, *SD* = 4.66 | Petersen[128] | *M* =27.38, *SD* = 1.53 | | | Observ. | **Exclusion:** History of systemic or neurological disease including cerebrovascular disease, past or current psychiatric illness, TBI, former intracranial surgery, history of alcoholism or drug abuse, untreated medical or metabolic condition, general anesthesia in the last 12 months, uncorrected hearing and vision problems |
| Burton et al.[146] | BC | 92 | *M* = 79.21, *SD* = 5.31 | | | *M* = 13.29 *SD* = 2.80 | Winblad et al.[147] | *M* =28.45, *SD* = 1.34 | | | Cross-sect data extrac long | **Exclusion:** Diagnosis of dementia, history of significant head injury, other neurological or major medical illnesses (e.g., heart disease, cancer, and PD), severe sensory impairment, extensive substance abuse, current psychiatric diagnoses or use of psychotropic drugs |
| Clément et al.[148] | Québec | 10 | *M* = 67.2, *SD* = 8.03 | F: 7 (70%) M: 3 (30%) | | *M* = 13.7, *SD* = 3.8 | Petersen[122] | *M* = 27.6, *SD* = 1.65 | | GDS-15: *M* = 3.29, *SD* = 2.98 | Observ. | **Exclusion:** Presence of any significant medical, neurological, or psychiatric condition that may explain cognitive impairment |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clément et al.[149] | Québec | 30 | *M* = 65.97, *SD* = 10.43 | F: 16 (53.33%) M: 14 (46.67%) | | *M* = 14.5, *SD* = 4.66 | Petersen[128] | *M* =28.63, *SD* = 1.16 | | | Observ. | **Exclusion:** A diagnosis of probable AD and other forms of dementia, history of neurological or severe psychiatric disorder, cardiovascular disease, alcoholism, drug addiction, using psychoactive drug or general anesthesia in the past 6 months |
| Hudon et al.[150] | Québec | 20 | *M* = 66.1, *SD* = 7.6 | F: 9 (45%) M: 11 (55%) | | *M* = 14.6, *SD* = 4.2 | Petersen[27] | *M* = 27.9, *SD* = 1.8 | | GDS-5: *M* = 1.1, *SD* = 1.3 | Observ. | **Exclusion:** history of TBI, stroke or transitory cerebral ischemia, former intracranial surgery, history of neurological disorder of cerebral origin or associated with another form of dementia (e.g., MS, parkinsonism, frontotemporal dementia), history or current psychiatric illnesses based on DSM-IV criteria, alcoholism/drug addiction according to DSM-IV criteria, unstable metabolic or medical condition, general anesthesia in the past 12 months |
| Montero-Odasso et al.[151] | Ontario | 11 | *M* = 76.6, *SD* = 7.3 | F: 6 (54.55%) M: 5 (45.45%) | | *M* = 14.1, *SD* = 3.4 | Petersen[122] | *M* = 287 *SD* = 1.6 | *M* = 22.8 *SD* = 1.2 | | Observ. | **Exclusion:** Any gait disorder, including PD, previous stroke, clinical osteoarthritis in lower limbs joints, myopathy, or neuropathy, presence of depressive symptoms (≥ 5/15 on the GDS) |
| Montero-Odasso et al.[152] | Ontario | 55 | *M* = 77.7, *SD* = 5.89 | F: 25 (45.45%) M: 30 (54.55%) | | *M* = 12.1, *SD* = 3.4 | Petersen[128] | *M* = 26.8, *SD* = 2.1 | *M* = 22.4, *SD* = 3.2 | | Observ. | **Exclusion:** An objective gait disorder due to PD, previous stroke, clinical osteoarthritis in lower limb joints, myopathy, or neuropathy, depressive symptoms ( ≥5/15 on the GDS) |
| Taler et al.[37] | Québec | 20 | *M* = 75.8, *SD* = 7.62 | F: 10 (50%) M: 10 (50%) | | *M* = 12.45, *SD* = 2.72 | Petersen[122] | *M* =27.36, *SD* = 2.27 | | | Observ. | No mention of exclusion criteria |
| Villeneuve et al.[153] | Québec | 68 | *M* = 70.65, *SD* = 8.66 | F: 39 (57.35%) M: 29 (42.65%) | Caucasian: 68 (100%) | *M* = 14.51, *SD* = 4.4 | Petersen[154] | *M* =27.53, *SD* = 2.2 | | | Observ. | **Exclusion:** General anesthesia in the past 6 months, history of neurological disease or event (i.e., stroke, PD, epilepsy, brain anoxia), psychiatric disorder (schizophrenia, MDD, alcoholism), or TBI |
| Arsenault-Lapierre et al.[155] | Québec | 42 | *M* = 76.2, *SD* = 7.2 | F: 18 (42.86%) M: 24 (57.14%) | | *M* = 10.9, *SD* = 3.2 | Petersen[124] | *M* = 26.7, *SD* = 2.1 | | GDS: *M* = 6.9, *SD* = 5.6 | Observ. | **Exclusion:** Reversible causes of cognitive impairment |
| Bélanger et al.[156] | Québec | 20 | *M* = 72.7, *SD* = 6.8 | | | *M* = 13.6, *SD* = 4 | Petersen[135] | *M* = 27.4, *SD* = 2.1 | | GDS: *M* = 1, *SD* = 1 | Observ. | **Exclusion:** Any significant systemic, neurological or psychiatric conditions that may contribute to cognitive impairment |
| Clément & Belleville[157] | Québec | 26 | *M* = 67.85, *SD* = 8.71 | F: 15 (57.69%) M: 11 (42.31%) | | *M* = 14.47, *SD* = 3.95 | Petersen [120,124,147] | *M* =27.66, *SD* = 1.60 | | | Observ. | **Exclusion:** Presence of any significant systemic, neurological, or psychiatric conditions that may affect cognition |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clément et al.[158] | Québec | 12 | *M* = 67.83, *SD* = 7.49 | F: 9 (75%) M: 3 (25%) | | *M* = 13.25, *SD* = 3.96 | Petersen [122,128,147] | *M* =27.83, *SD* = 1.59 | | | Observ. | **Exclusion:** Presence of any medical, neurological or psychiatric illnesses that may contribute to cognitive impairment |
| Jean et al.[159] | Québec | 22 | *M* = 68.55, *SD* = 7.89 | F: 13 (59.09%) M: 9 (40.91%) | | *M* = 14.5, *SD* = 3.86 | Petersen [27,128] | *M* = 29.5, *SD* = 0.70 | | | RCT | **Exclusion**: Meeting diagnostic criteria for any dementia, any neurological or systemic problem known to impair cognition, current or past alcohol or drug abuse, chronic psychiatric illness or an acute episode of MDD, psychotropic or other meditation know to affect cognition (incl. cholinesterase inhibitor/cognition enhancer) |
| Joubert et al.[160] | Québec | 15 | *M* = 73.7, *SD* = 6.3 | F: 8 (53.33%) M: 7 (46.67%) | | *M* = 12.8, *SD* = 4.8 | Petersen[135] | *M* = 27.4, *SD* = 1.6 | | | Observ. | **Exclusion:** A history of systemic or neurological diseases (incl. cerebrovascular disease, past or current psychiatric illness, TBI, history of alcoholism, untreated medical or metabolic condition), general anesthesia in the past 12 months, or uncorrected hearing or vision impairment |
| McLaughlin et al.[161] | Ontario | 21 | *M* = 74.01, *SD* = 6.22 | F: 9 (42.86%) M: 12 (57.14%) | | *M* = 12.15, *SD* = 2.54 | Petersen[27] | *M* =27.21, *SD* = 2.66 | | | Observ. | **Exclusion:** Fluent in English, uncorrected vision, presence of neurological or psychiatric illness, stroke, head injury, alcohol or drug abuse, and depression |
| Montero-Odasso & Muir[162] | Ontario | 43 | *M* = 75.1, *SD* = 6.3 | F: 23 (53.49%) M: 20 (46.51%) | | *M* = 12.7, *SD* = 3.3 | Winblad et al.[147] | | *M* = 3.64, *SD* =0.89 | | Observ. | **Exclusion:** Inability to understand English, Parkinsonism, use of any psychotropic medication, or diagnosis of depression |
| Sylvain-Roy et al.[163] | Québec | 20 | *M* = 64.4, *SD* = 11.5 | F: 13 (65%) M: 7 (35%) | | *M* = 14, *SD* = 4.7 | Petersen[128] | *M* = 28, *SD* = 2.1 | | | Observ. | **Exclusion:** Uncorrected vision or hearing impairment, presence or history of alcoholism, severe psychiatric disorder, significant cerebrovascular disorder, neurological disorder, intellectual deficiency, presence of systemic illnesses that affect cognition, general anesthesia in the past 6 months, impairment hand motoricity |
| Arsenault-Lapierre et al.[164] | Québec | 39 | *M* = 72.5, *SD* = 8.6 | F: 22 (56.41%) M: 17 (43.59%) | | *M* = 13, *SD* = 3 | Petersen[124] | *M* = 28.1, *SD* = 1.5 | | GDS: *M* = 6; *SD* = 3.9 | Observ. | **Exclusion:** Serious health problem or systemic cause or other neurological illnesses that could account for cognitive impairment or chronic psychiatric disorder (other than depression) |
| Belleville et al.[165] | Québec | 15 | *M* = 70.13, *SD* = 7.34 | F: 11 (73.33%) M: 4 (26.67%) | | *M* = 13.73, *SD* = 4.33 | Petersen[128] | *M* =27.73, *SD* = 1.87 | | | Non-random training | **Exclusion:** Uncorrected vision and hearing, probable or possible AD, other forms of dementia, current or history of severe psychiatric disorder, cerebrovascular disease, neurological disorder or alcoholism, general anesthesia in the past 6 months, use of psychotropic medication, presence of MRI exclusion criteria |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Belleville et al.[166] | Québec | 28 | *M* = 70.9, *SD* = 6.5 | | | *M* = 13.7, *SD* = 3.8 | Petersen[135] | *M* = 27.8, *SD* = 1.4 | | | Observ. | **Exclusion:** Alcohol or substance addiction, presence of history of severe psychiatric disorder (i.e., MDD or schizophrenia), dyslexia, intellectual deficiency, significant cerebral disorder, neurological disorder, general anesthesia in the last 6 months, use of medication known to affect memory, individuals with significant musical expertise |
| Brunet et al.[167] | Québec | 33 | *M* = 72.83, *SD* = 7.52 | F: 16 (48.48%) M: 17 (51.52%) | | *M* = 13.00, *SD* = 5.11 | Petersen[27] | | *M*=23.33, *SD* = 2.7 | GDS: *M* = 9.15, *SD* = 2.87 | Observ. | **Exclusion:** A history of neurological disease, including cerebrovascular disease, past or current psychiatric disorders other than major depression, TBI, alcoholism, untreated medical or metabolic condition, general anesthesia in the past 12 months, ECT in the past 12 months, former intracranial surgery, uncorrected hearing and vision problems |
| Gagnon & Belleville[168] | Québec | 20 | *M* = 73.4, *SD* = 6.89 | | | *M* = 15.9, *SD* = 4.1 | Gauthier et al.[169] | *M* =27.95, *SD* = 1.5 | | | Observ. | **Exclusion:** Alcoholism, general anesthesia in the past 6 months, presence of history of severe psychiatric disorders, neurological disorders, cerebrovascular disorder or stroke |
| Gao et al.[170] | Ontario | 23 | *M* = 70.2, *SD* = 6.8 | F: 10 (43.48%) M: 13 (56.52%) | | *M* = 14.3, *SD* = 3.2 | Petersen[122] | *M* = 27.3, *SD* = 2.4 | | | Observ. | **Exclusion:** Secondary causes of dementia, comorbid neurological or psychiatric illness |
| Hudon et al.[171] | Québec | 23 | *M* = 66.8, *SD* = 8.8 | F: 9 (39.13%) M: 14 (60.87%) | | *M* = 14.6, *SD* = 4.2 | Petersen[27] | *M* = 27.7, *SD* = 2 | | GDS-5: *M* = 1.1, *SD* = 1.4 | Observ. | **Exclusion:** History of TBI, stroke or transitory cerebral ischemia, former intracranial surgery, neurological disorder of cerebral original or other dementia (e.g., MS, parkinsonism, frontotemporal dementia), psychiatric illness, current or history of alcoholism or drug addiction, unstable metabolic or medical condition, general anesthesia in the past 6 months |
| Matteau et al.[172] | Québec | 22 | *M* = 70, *SD* = 6.8 | F: 12 (54.55%) M: 10 (45.45%) | | *M* = 13.7, *SD* = 4.4 | Petersen [27,147] | *M* = 28.8, *SD* = 1.8 | | HAMD: *M* = 4.3, *SD* = 3.5 | Observ. | **Exclusion:** acute episode of MDD determined by HAMD (scores > 13), any neurological or systemic problem other than PD and AD known to affect cognition (e.g., TBI, tumor), deep brain stimulation or other brain neurosurgery, current or past alcohol or drug abuse, chronic psychiatric illness |
| Muir et al.[173] | Ontario | 29 | *M* = 73.6, *SD* = 6.2 | F: 17 (58.62%) M: 12 (41.38%) | | *M* = 11.9, *SD* = 2.9 | Winblad et al.[147] | *M* = 27.5, *SD* = 1.9 | *M* = 23.4, *SD* = 2.8 | | Observ. | **Exclusion:** Inability to understand English, falls in the past year, Parkinsonism or other neurological disorder with residual deficits, musculoskeletal disorder affecting gait performance, use of psychotropic medication, and MDD |
| Protzner et al.[174] | Ontario | 14 | *M* = 68.6, *SD* = 7.4 | F: 7 (50%) M: 7 (50%) | | *M* = 13.4, *SD* = 2.8 | Petersen[128] | *M* = 27.7, *SD* = 1.1 | | | Observ. | **Exclusion:** Secondary causes of MCI (i.e., vascular, metabolic, nutritional, or mood disorders) |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rupsingh et al.[175] | Ontario | 12 | *M* = 71.8, *SD* = 9.9 | F: 5 (41.67%) M: 7 (58.33%) | | *M* = 18, *SD* = 5.4 | Petersen[128] | *M* = 27.6, *SD* = 1.9 | | | Observ. | **Exclusion:** Contraindications to MRI, clinical depression, substance abuse, diagnosis of other dementia or presence of significant vascular disease or cerebrovascular infarcts |
| Sherwin et al.[176] | Québec | 28 | *M* = 75.93, *SD* = 6.55 | M: 28 (100%) | | *M* = 11.63, *SD* = 4.33 | Petersen[122] | *M* =27.46, *SD* = 2.22 | | | RCT | **Exclusion**: Uncontrolled hypertension, abnormal clotting, hypercoagulable states, sleep apnea, carcinoma of the prostate, hypercalcemia, metabolic disease, severe COPD, renal insufficiency, liver disease, unstable coronary artery disease, history of cerebrovascular accident, recent classical migraines, thrombophlebitis or thromboembolic disease, currently taking Coumadin anti-diabetic medications, cholinesterase inhibitors or other cognitive enhancer medications (e.g., gingko biloba, vitamin E) |
| Vandermorris et al.[177] | BC | 77 | | | Caucasian: 77 (100%) | | Winblad et al.[147] | *M* = 28.6, *SD* = 1.3 | | | Prospect long | **Exclusion:** Diagnosed dementia or MMSE <24, a history of significant head injury (loss of consciousness >5), other neurological or major medical illnesses, severe sensory impairment, alcohol or substance abuse, current psychiatric diagnosis, psychotropic drug use, and not fluent in English |
| Villeneuve et al.[178] | Québec | 44 | *M* = 72.67, *SD* = 7.19 | F: 23 (52.27%) M: 21 (47.73%) | | *M* = 13.6, *SD* = 5.14 | Petersen[154] | *M* =27.66, *SD* = 1.72 | | | Observ. | **Exclusion:** Dementia, history of temporal lobe epilepsy or other neurological disorders (PD), alcoholism, major psychiatric disease, presence of a stroke or large vessel disease, history of stroke, TBI, general anesthesia in the past 6 months. |
| Xie et al.[43] | Québec | 187 | *M* = 80, *SD* = 6 | F: 101 (54.01%) M: 86 (45.99%) | | ≤ 12 years: n = 56; > 12 years: n = 80; 51 missing cases | Petersen [27,122] | *M* = 26.6, *SD* = 2 | | | Observ. | **Exclusion:** Participants with less than 2 MMSE scores |
| Arsenault-Lapierre et al.[179] | Québec | 60 | *M* = 75, *SD* = 7 | | | *M* = 11.2, *SD* = 3.1 | Petersen[120] | *M* = 27.1, *SD* = 2.2 | | GDS: *M* = 6.7, *SD* = 4.9 | Observ. | **Exclusion:** Reversible causes of cognitive dysfunction |
| Arsenault-Lapierre et al.[180] | Québec | 21 | *M* = 77.1, *SD* = 1.3 | F: 7 (33.33%) M: 14 (66.67%) | | *M* = 15.9, *SD* = 1.0 | Petersen[124] | *M* = 27.8, *SD* = 2 | *M* = 23.5, *SD* = 0.7 | | Observ. | **Exclusion:** Medical or psychiatric disorder that may account for cognitive impairment |
| Barnabe et al.[38] | Québec | 20 | *M* = 76.4, *SD* = 6.87 | F: 8 (40%) M: 12 (60%) | | *M* = 14.6, *SD* = 4.3 | Petersen [27,122] | *M* =28.35, *SD* = 1.46 | | | Observ. | No mention of exclusion criteria |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brambati et al.[39] | Québec | 13 | *M* = 72.7, *SD* = 4.9 | F: 7 (53.85%) M: 6 (46.15%) | | *M* = 14.8, *SD* = 3.9 | Petersen[122] | *M* = 28.7, *SD* = 1.1 | | GDS: *M* = 3.6, *SD* = 2.3 | Observ. | No mention of exclusion criteria |
| Clément & Belleville[181] | Québec | 26 | *M* = 67.85, *SD* = 8.70 | F: 15 (57.69%) M: 11 (42.31%) | | *M* = 14.47, *SD* = 3.95 | Petersen[122,128,147] | *M* =27.66, *SD* = 1.60 | | | Observ. | **Exclusion:** Any significant medical, neurological, or psychiatric conditions that may contribute to cognitive difficulties |
| Gagnon & Belleville[182] | Québec | 24 | *M* = 67.71, *SD* = 7.12 | | | *M* = 14.04, *SD* = 5.28 | Petersen[122] | *M* =27.96, *SD* = 1.35 | | GDS: *M* = 3.34, *SD* = 2.25 | RCT | **Exclusion**: alcoholism, general anaesthesia in the past 6 months, presence or history of severe psychiatric disorders, TBI, depression, neurological disorders, or stroke, dementia |
| Morin et al.[183] | Québec | 12 | *M* = 71.2, *SD* = 6.19 | F: 6 (50%) M: 6 (50%) | | *M* = 14.65, *SD* = 5.55 | Petersen[27] | | *M* = 23.6, *SD* =3.53 | GDS: *M* = 8, *SD* = 1.79 | Observ. | **Exclusion:** History of TBI, presence of significant vascular risk, former intracranial surgery, neurological disorder (e.g., dementia, MS, parkinsonism, frontotemporal dementia); unstable metabolic or medical condition (e.g., uncontrolled diabetes, hypothyroidism), general anesthesia in the past 12 months, contraindication for MRI, past or current diagnosis of MDD |
| Rainville et al.[184] | Québec | 81 | *M* = 69.83, *SD* = 8.20 | | | *M* = 14.65, *SD* = 4.16 | Petersen[135] | *M* =,27.74 *SD* = 1.65 | | GDS: *M* = 3.47, *SD* = 2.93 | Observ. | **Exclusion**: alcoholism, presence or history of severe psychiatric disorder, neurological disorder or stroke, general anesthesia in the past 6 months, and MDD |
| Troyer et al.[185] | Ontario | 24 | *M* = 76.1, *SD* = 7.6 | F: 15 (62.5%) M: 6 (37.5%) | | *M* = 14.2, *SD* = 2.5 | Knopman et al.[186] | *M* = 27.4, *SD* = 1.8 | | HADS-Depression: *M* = 3, *SD* = 2.6 | Observ. | **Exclusion:** Medical or psychiatric conditions that may account for memory impairment |
| Villeneuve & Belleville[187] | Québec | 49 | *M* = 71.6, *SD* = 7.1 | F: 25 (51.02%) M: 24 (48.98%) | | *M* = 13.3, *SD* = 4.9 | Petersen[154] | *M* = 27.8, *SD* = 1.6 | | | Observ. | **Exclusion:** Dementia, alcoholism, presence of a stroke or large vessel disease on the MRI, history of stroke, TBI, and general anesthesia in the past 6 months |
| Ansado et al.[188] | Québec | 11 | *M* = 73.7, *SD* = 6.3 | F: 5 (45.45%) M: 6 (54.55%) | | *M* = 12.8, *SD* = 4.8 | Petersen[128] | *M* = 27.4, *SD* = 1.6 | | | Observ. | **Exclusion:** History of systemic or neurological disease, past or current psychiatric illness, TBI, history of alcoholism, untreated medical or metabolic condition, general anesthesia in the past 12 months, uncorrected hearing or vision problems |
| Clément et al.[189] | Québec | 24 | *M* = 68.42, *SD* = 9.27 | F: 14 (58.33%) M: 10 (41.67%) | | *M* = 14.5, *SD* = 4.17 | Petersen[122,128,147] | *M* =27.96, *SD* =1.78 | | | Observ. | **Exclusion:** Any significant systemic, neurological or psychiatric condition that may contribute to cognitive impairment |
| Gu et al.[44] | Ontario | 20 | *M* = 66.95 | | | *M* = 15 (*n* = 17) | NIA-AA[18] | *M* = 28.25 | | | Observ. | **Exclusion:** Reversible causes of dementia (TSH, B12, folate deficiency) |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Konsztowicz et al.[46] | Québec | 19 | *M* = 78.21, *SD* = 6.34 | F: 10 (52.63%) M: 9 (47.37%) | | *M* = 11.16, *SD* = 6.16 | Petersen[122] | *M* =26.79, *SD* = 2.54 | *M*=20.79, *SD* =3.68 | GDS: *M* = 2.63, *SD* = 1.89 | Rand feasibil | **Exclusion:** Inability to comply with treatment program due to significant comorbid illness or an anticipated inability to attend all study sessions |
| Guild et al.[190] | Ontario | 14 | *M* = 73.07, *SD* = 6.44 | F: 12 (85.71%) M: 2 (14.29%) | | *M* = 14.57, *SD* = 1.83 | Petersen[124] | *M* =28.14, *SD* = 1.46 | | | Observ. | **Exclusion:** Learned English after the age of 5, psychiatric or medical condition that may account for memory impairment (i.e., prior history of neurological disorder, head injury, dementia, stroke), heart attack, diabetes, anxiety, or psychiatric disorder, normal or controlled cholesterol and thyroid function |
| Julayanont et al.[191] | Québec | 165 | *M* = 73.94, *SD* = 0.88 | F: 107 (64.85%) M: 58 (35.15%) | | *M* = 10.53, *SD* = 0.45 | Petersen[122] | | *M*=20.18, *SD* = 0.3 | | Retro chart review | **Exclusion:** Moderate to severe white matter disease or other causes of cognitive impairment on the computed tomography or magnetic resonance imaging |
| McLaughlin et al.[192] | Québec | 16 | *M* = 76.2, *SD* = 5.3 | F: 6 (37.5%) M: 10 (62.5%) | Caucasian: 14 (87.5%); Non-Caucasian: 2 (12.5%) | *M* = 14.9, *SD* = 2.9 | Petersen[27] | *M* = 27.4, *SD* = 1.6 | | HADS-Depression: *M* = 2.8, *SD* = 2.7 | Observ. | **Exclusion:** History of stroke, TIA, neurological or psychiatric illness, head injury, substance abuse, elevated scores on the HADS, uncorrected visual impairment, or significant hearing impairment |
| Peltsch et al.[193] | Ontario | 22 | *M* = 76, *SD* = 8 | F: 12 (54.55%) M: 10 (45.45%) | | *M* = 14, *SD* = 4 | Petersen[124] | *M* = 27, *SD* = 2 | | | Observ. | **Exclusion:** Uncorrected visual impairment, visual or psychiatric symptoms other than AD and aMCI |
| Peters et al.[194] | Québec | 40 | *M* = 72.53, *SD* = 6.84 | F: 23 (57.5%) M: 17 (42.5%) | | *M* = 13.36, *SD* = 5.05 | Petersen[154] | *M* =27.70, *SD* = 1.72 | | | Observ. | **Exclusion:** Alcoholism, general anesthesia in the last 6 months, presence or history of severe psychiatric disorder, intellectual disability, neurological disease or event (e.g., stroke, PD, epilepsy, brain anoxia), psychiatric disorder (e.g., schizophrenia, MDD), TBI, or systemic disease that may impair cognition |
| Wu et al.[195] | Québec | 13 | *M* = 69, *SD* = 5.69 | F: 7 (53.85%) M: 6 (46.15%) | | *M* = 13.15, *SD* = 3.02 | Petersen[27] | *M* =26.23, *SD* = 2.05 | | | Observ. | **Exclusion:** Neurological disease (e.g., stroke, PD, other neurodegenerative diseases), presence of any major structural abnormalities or signs of major vascular pathology; Axis 1 psychiatric disorder or intellectual disability, use of psychoactive substance, previous or present use of cholinesterase inhibitor |
| Callahan et al.[196] | Québec | 35 | *M* = 73.19, *SD* = 7.32 | F: 16 (45.71%) M: 16 (45.71%) | | *M* = 12.88, *SD* = 5.11 | Petersen[27] | | *M*=23.16, *SD* =2.55 | GDS: *M* = 9.09, *SD* = 3.05 | Observ. | **Exclusion:** History of neurological and cerebrovascular disease, past or current psychiatric illness (other than MDD), TBI, history of alcoholism, untreated medical or metabolic conditions, general anesthesia or ECT in the past 12 months, past intracranial surgery, uncorrected hearing or visual impairment |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cloutier et al.[197] | Québec | 121 | *M* = 70.54, *SD* = 8.21 | F: 74 (61.16%) M: 47 (38.84%) | | *M* = 14.46, *SD* = 4.16 | Petersen[128,147] | *M* =27.23, *SD* = 2.22 | | GDS: *M* = 15.00, *SD* = 3.66 | Long | **Exclusion:** Uncorrected vision or hearing impairment, currently on AD-related medication, long time use of anxiolytics and antidepressant, severe diagnosis of any severe psychiatric disorder, current major medical condition, current or past alcohol or substance abuse, significant cerebrovascular, neurological, or neurodegenerative disorders, stroke, or large-vessel disease, or general anesthesia within the last 6 months |
| Gaudreau et al.[198] | Québec | 30 | *M* = 73.9, *SD* = 6.1 | F: 18 (60%) M: 12 (40%) | | *M* = 13.6, *SD* = 5.3 | NIA-AA[18] | | *M* = 23, *SD* = 3.2 | GDS: *M* = 6.8, *SD* = 4.6 | Observ. | **Exclusion:** History of TBI, stroke or other cerebrovascular disease, delirium (in the past 6 months), formal intracranial surgery, neurological disorder of cerebral original or another dementia state, encephalitis or bacterial meningitis, unstable metabolic or medical condition, current or past diagnosis of psychiatric illness or dementia according to DSM-IV, oncological treatment in the past 12 months, substance addiction according to the DSM-IV, general anaesthesia in the last 6 months, uncorrected vision or hearing problem, use of experimental medication |
| Le Page et al.[199] | Québec | 10 | *M* = 72.9, *SD* = 6.42 | F: 9 (90%) M: 1 (10%) | | | Grundman et al.[200] | *M* = 27.8, *SD* = 1.99 | *M*=24.3, *SD* =2.06 | | Observ. | **Exclusion:** History or physical signs of atherosclerosis or inflammation |
| Sheldon et al.[40] | Ontario | 16 | *M* = 75.1, *SD* = 5.7 | F: 6 (37.5%) M: 10 (62.5%) | | *M* = 15, *SD* = 2.9 | Petersen[27] | | *M* = 28.4, *SD* = 1.2 | HADS-Depression: *M* = 3.3, *SD* = 2.6 | Observ. | No mention of exclusion criteria. |
| ten Brinke et al.[201] | British Columbia | 39 | *M* = 75.15, *SD* = 3.74 | F: 39 (100%) | | Grade 9-12 without certificate = 5; High school diploma = 10; Trade or professional certificate or diploma = 5; University certificate or diploma = 8; University degree = 11 | Petersen[122] | *M* =27.15, *SD* = 2.05 | *M*=22.09, *SD* =3.19 | GDS: *M* = 0.77, *SD* = 1.46 | RCT | **Exclusion:** Current medication for which exercise is contraindicated, participated regularly in resistance training or aerobic training in the last 6 months, neurodegenerative disease/stroke, psychiatric diagnosis, dementia of any type, inability to speak or understand English fluently, ERT |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brayet et al.[202] | Québec | 32 | *M* = 63.96, *SD* = 6.97 | F: 10 (31.25%) M: 22 (68.75%) | | *M* = 12.53, *SD* = 3.67 | NIA-AA[18] | *M* =27.51, *SD* = 2.13 | | | Observ. | **Exclusion:** dementia according to DSM-5, sleep apnea, narcolepsy, excessive daytime sleepiness, REM sleep behaviour disorder, major psychiatric disorder, substance abuse, history of stroke or brain injury, uncontrolled hypertension or diabetes, COPD, brain tumour, encephalitis, or EEG abnormalities suggestive of epilepsy |
| Burhan et al.[203] | Ontario | 10 | *M* = 72.7, *SD* = 9.3 | F: 10 (100%) | | *M* = 10.5, *SD* = 0.8 | Petersen[124] | | *M* = 22.2, *SD* = 2.5 | GDS-15: *M* = 2.6, *SD* = 2.7 | Observ. | **Exclusion:** neurodegenerative illness (any form of dementia or PD) stroke, TBI, epilepsy, any major mental illness (e.g., MDD, bipolar disorder, schizophrenia, or substance disorder), currently on any cognitive enhancers |
| Callahan et al.[204] | Québec | 54 | *M* = 74.44, *SD* = 6.07 | F: 28 (51.85%) M: 26 (48.15%) | | *M* = 13.49, *SD* = 5.19 | Petersen[27] | | *M*=23.37, *SD* =3.42 | *M* = 6.67, *SD* =2.59 | Observ. | **Exclusion**: history of neurological disease, TBI, stroke, psychiatric illness (other than depression), substance abuse, untreated metabolic condition, uncorrected visual/ auditory impairment, intracranial surgery, nor general anaesthesia or oncological treatment in the past 6 months |
| Davidson et al.[41] | Ontario | 19 | *M* = 75.63, *SD* = 6.23 | F: 10 (52.63%) M: 9 (47.37%) | | *M* = 16.68, *SD* = 3.96 | Petersen[122] | | *M*=22.79, *SD* =3.09 | | Observ. | No mention of exclusion criteria. Excluded one participant with poor hearing, one with very low MoCA score (11/30), and three individuals who developed dementia (2 with Alzheimer's disease and 1 fronto-temporal dementia) from data analyses |
| Langlois et al.[205] | Québec | 20 | *M* = 77, *SD* = 6.5 | F: 14 (70%) M: 6 (30%) | | *M* = 15, *SD* = 4.4 | NIA-AA[18] | | *M* = 26, *SD* = 2.4 | | Observ. | **Exclusion:** History of systemic or neurological disease, TBI, psychiatric illness, history of alcohol or drug abuse, untreated medical or metabolic condition, general anesthesia in the past 6 months |
| Nasreddine & Patel[206] | Québec | 25 | *M* = 72.69 | | | | Petersen[27] | | *M*=21.24, SD =3.57 | | Observ. | **Exclusion:** History of central nervous system disorder, or any condition that may account for cognitive deficit, no learning disability, attention deficit disorder, or mental retardation, no physical disability that would influence test results, not pre-existing or current psychiatric illnesses (except for those who with previous depression without hospitalization and has a GDS score of less than 6 in the last 6 months), on any unstable dose of medication that affects the central nervous system, currently on antiepileptic medication, neuroleptics, must not have a score greater than 7 on the subjective memory scale, alcohol consumption exceeding the permitted limit (3 or more 200 ml drinks of 5 to 7% alcohol per day for men; and 2 or more 200ml drinks of 5 to 7% of alcohol per day for women, and 1 or more 200ml drink of 35% alcohol per day for men and women, consumed drugs in the past 5 years. |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teasdale et al.[30] | Québec | 15 | *M* = 71.1, *SD* = 9 | F: 2 (13.33%) M: 13 (86.67%) | | *M* =14.3, *SD* = 2.5 | NIA-AA[18] | | *M* = 24.3, *SD* = 2.5 | GDS: *M* = 4.8, *SD* = 3.8 | Observ. | No mention of exclusion criteria |
| Vallet et al.[207] | Québec | 16 | *M* = 78.19, *SD* = 6.1 | F: 11 (68.75%) M: 5 (31.25%) | | *M* = 14.94, *SD* = 4.10 | Petersen [18,23] | *M* =28.31, *SD* = 1.5 | *M*=25.62, *SD* = 2.1 | | Observ. | **Exclusion:** Medical history of or currently taking medications for conditions with known sensory or neurological effects; participants with diagnoses of depression and/or anxiety were included if they were stable on medication or non-symptomatic at the time of study |
| Bocti et al.[208] | Québec | 42 | *M* = 69.62, *SD* = 9.31 | F: 20 (47.62%) M: 22 (52.38%) | | *M* = 12.27, *SD* = 5.07 | Chertkow et al.[130] | *M* =27.93, *SD* = 1.83 | *M*=23.22, *SD* =3.86 | | Cross-sect | **Exclusion:** severe psychiatric or systemic disorder, cognitive impairment attributed to large vessel stroke, TBI, alcohol abuse, sleep apnea, or cancer and related treatment |
| Callahan et al.[209] | Québec | 58 | *M* = 73.93, *SD* = 6.67 | F: 29 (50%) M: 29 (50%) | | *M* = 13.54, *SD* = 3.98 | Petersen[27] | | *M*=23.69, *SD* =3.03 | GDS: *M* = 6.85, *SD* = 2.19 | Observ. | **Exclusion:** History of neurological disease, brain injury, stroke, psychiatric illness (other than depression), substance abuse, general anesthesia, intracranial surgery or oncologic treatment in the past 6 months, or untreated metabolic conditions, or uncorrected visual/auditory impairment |
| Crockett et al.[210] | British Columbia | 40 | *M* = 76.75, *SD* = 5.8 | F: 21 (52.5%) M: 19 (47.5%) | | | Petersen[122] | *M* = 27.5, *SD* = 1.3 | *M* = 22.3, *SD* = 2.7 | | Cross-sect | **Exclusion:** Formal diagnosis of neurodegenerative disease, stroke, dementia of any type, or psychiatric conditions, clinically significant neuropathy or severe musculoskeletal or joint disease, currently on psychotropic medication, have a history of carotid sinus sensitivity, living in a nursing home, extended care facility, or assisted-care facility, ineligible for MRI scanning |
| Hird et al.[31] | Ontario | 24 | *M* = 66.5, *SD* = 9.5 | F: 10 (41.67%) M: 14 (58.33%) | | *M* = 15, *SD* = 2.6 | NIA-AA[18] | | *M* = 23.8, *SD* = 1.9 | | Observ. | No mention of exclusion criteria |
| Knezevic et al.[211] | Ontario | 11 | *M* = 71.91, *SD* = 5.3 | F: 6 (54.55%) M: 5 (45.45%) | | *M* = 15.82, *SD* = 2.36 | Petersen[27] | *M* = 27.3, *SD* = 1.95 | *M* = 21.7, *SD* = 3.6 | | Observ. | **Exclusion:** Concurrent Axis I DSM-IV disorder, history of closed head injury with loss of consciousness, stroke, or other neurological disorder with central nervous system involvement |
| Le Page et al.[212] | Québec | 13 | *M* = 72.8, *SD* = 3.64 | F: 9 (69.23%) M: 4 (30.77%) | | | Grundman et al.[200] | *M* =26.75, *SD* = 1.5 | *M* =24, *SD* =2.95 | | Observ. | **Exclusion:** History or physical signs of atherosclerosis or inflammation |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mah et al.[213] | Ontario | 16 | *M* = 73.5, *SD* = 7 | F: 13 (81.25%) M: 3 (18.75%) | Caucasian: 16 (100%) | *M* = 15.6, *SD* = 3.5 | Petersen[124] | *M* = 27.8, *SD* = 1.6 | | GDS: *M* = 2.1, *SD* = 2.8 | Observ. | **Exclusion:** Inability to speak/understand English, MMSE score < 26, history of neurological disorder, unstable medical conditions, currently taking psychotropic medication |
| Montero-Odasso et al.[214] | Ontario | 112 | *M* = 75.97, *SD* = 6.88 | F: 55 (49.11%) M: 57 (50.89%) | | | Petersen[128,147] | *M* =27.46, *SD* = 2.46 | *M*=23.14, *SD* =3.39 | | Prospect cohort | **Exclusion**: Inability to speak/understand English, any neurological condition/disease with motor deficits, musculoskeletal disorder of lower limbs affecting gait performance, use of neuroleptics or benzodiazepines, MDD |
| O'Caoimh et al.[215] | Ontario | 766 | *M* = 75.30, *SD* = 7.43 | F: 403 (52.61%) M: 363 (47.39%) | | *M* = 12, *SD* = 2.97 | Petersen[122] | SMMSE: *M* =27.65, *SD* = 2.23 | | | Observ. | **Exclusion:** Missing demographic information, any dementia, active depression, or unclear diagnosis; individuals with missing data in key measures were also excluded |
| Belleville et al.[216] | Québec | 127 | *M* = 72.19, *SD* = 7.28 | F: 70 (55.12%) M: 57 (44.88%) | | *M* = 14.67, *SD* = 3.85 | Petersen[128] | | *M*=24.44, *SD* =3.02 | GDS: *M* = 3.27, *SD* = 3.05 | Single blind RCT | **Exclusion:** Current psychiatric, cerebrovascular or neurological disorder, substance abuse, general anesthesia in the past 6 months, significant physical mobility impairment, probable or possible dementia, MMSE < 24, cognitive impairment significantly impacting functional independence |
| Croteau et al.[217] | Québec | 20 | *M* = 76.9, *SD* = 5.8 | F: 11 (55%) M: 9 (45%) | | | Petersen[27] | *M* = 27.5, *SD* = 2 | | | Observ. | **Exclusion:** smoking, substance abuse, untreated or uncontrolled hypertension, dyslipidemia, diabetes |
| Duncan et al.[45] | Québec | 68 | *M* = 73.65, *SD* = 1.00 | F: 32 (47.06%) M: 36 (52.94%) | | *M* = 12.4, *SD* = 0.71 | Gauthier et al.[169] adapted from Petersen[128] | | *M*=27.15, *SD* =0.36 | | Observ. | **Exclusion:** Left-handedness, cognitive function reverting to "normal" after initial MCI diagnosis |
| Goodman et al.[218] | Ontario | 34 | *M* = 74.8, *SD* = 5.9 | F: 18 (52.94%) M: 16 (47.06%) | Caucasian: 23 (68%); Non-Caucasian: 11 (32%) | *M* = 15.2, *SD* = 2.3 | DSM-5[219] | *M* = 27.6, *SD* = 3.1 | | | Observ. | **Exclusion:** Age <60 years, MADRS ≥ 10, DSM-5 criteria for MDD in the past 10 years, lifetime diagnosis of schizophrenia, bipolar disorder, or OCD, diagnosis of alcohol or other substance use disorder within the last 12 months, significant neurological condition, use of cognitive enhancer medication within the past 6 weeks, MoCA < 26, MMSE < 24 |
| Hsu et al.[220] | BC | 49 | *M* = 75.4, *SD* = 6.3 | F: 30 (61.22%) M: 19 (38.78%) | | | NIA-AA[18] | *M* = 27.6, *SD* = 1.4 | *M* = 22.3, *SD* = 2.6 | | Cross-sect | **Exclusion:** Formal diagnosis of neurodegenerative disease, stroke, any dementia, psychiatric condition, clinically significant neuropathy or severe musculoskeletal or joint disease, taking psychotropic medication or medications that may affect cognition, not expected to start or are stable on fixed dose of antidementia medication in the 12-month study period, a history of carotid sinus sensitivity, living in a nursing home, extended care facility, or assisted-care facility, ineligible for MRI scanning |

**Appendix B.** Continued

| Article | Province | Sample Size | Age | Sex | Race/ Ethnicity | Education | Diagnostic Criteria | MMSE | MoCA | Depression Measure(s) | Study Design | Inclusion/ Exclusion Criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *MCI-PD Articles* | | | | | | | | | | | | |
| Matteau et al.[172] | Québec | 22 | *M* = 68.3, *SD* = 9.3 | F: 10 (45.45%) M: 12 (54.55%) | | *M* = 13.1, *SD* = 4.5 | Petersen [27,147] | *M* = 27.8, *SD* = 1.4 | | HAMD: *M* = 4.0, *SD* = 3.1 | Observ. | **Exclusion:** Acute episode of MDD determined by HAMD (scores > 13), any neurological or systemic problems other than PD and AD known to affect cognition (e.g., TBI, tumour), deep brain stimulation or other brain neurosurgery, current or past alcohol or drug abuse, chronic psychiatric illness |
| Villeneuve et al,[221] | Québec | 18 | *M* = 67.72, *SD* = 7.71 | | | *M* = 15.06, *SD* = 3.99 | Petersen[154] | *M* =28.39, *SD* = 0.98 | | | Observ. | **Exclusion:** Dementia or MDD according to DSM-IV-TR, sleep apnea index > 20, abnormal EEG suggestive of epilepsy, unstable diabetes or hypertension, encephalitis, age > 90, language other than French or English, primary school uncompleted |
| Hanganu et al.[32] | Québec | 18 | *M* = 64.7, *SD* = 4.5 | F: 5 (27.78%) M: 13 (72.22%) | | *M* = 13.4, *SD* = 3.2 | The Movement Disorder Society Task Force[222] | | *M* = 26.5, *SD* = 1.6 | | Observ. | No mention of exclusion criteria |
| Christopher et al.[223] | Ontario | 11 | *M* = 70.8, *SD* = 7.01 | F: 3 (27.27%) M: 8 (72.73%) | | *M* = 16.2, *SD* = 1.47 | The Movement Disorder Society Task Force[222] | | *M* = 23.2, *SD* =2.79 | BDI-II: *M* = 5.54, *SD* = 5.87 | Observ. | **Exclusion:** any other neurological or psychiatric condition, dementia |
| Hanganu et al.[224] | Québec | 17 | *M* = 64.01, *SD* = 5.36 | F: 6 (35.29%); M: 11 (64.71%) | | *M* = 13.47, *SD* = 3.37 | The Movement Disorder Society Task Force[222] | | *M*=26.25, *SD* =2.02 | | Observ. | **Exclusion:** Evidence of cognitive abnormalities not attributed to age. |
| Nagano-Saito et al.[33] | Québec | 14 | *M* = 63.7, *SD* = 5.01 | F: 5 (35.71%) M: 9 (64.29%) | | *M* = 12.9, *SD* = 2.46 | The Movement Disorder Society Task Force[222] | | *M* = 26.5, *SD* =1.79 | BDI-II: *M* = 11.1, *SD* = 6.57 | Observ. | No mention of exclusion criteria |
| *MCI-VD Article* | | | | | | | | | | | | |
| Gu et al.[44] | Ontario | 20 | *M* = 66.15 | | | *M* = 14.45 | NIA-AA[18] along with imaging data | *M* = 27.56 | | | Observ. | **Exclusion:** Reversible causes of dementia (TSH, B12, folate deficiency) |

Study Designs: RCT = randomized control trial; Observ. = observational; Prospect cohort = prospective cohort; N-rand feasibil = non-randomized feasibility; Cross-sect = cross-sectional; Prospect long = prospective longitudinal; Cross-sect data extrac long = Cross-sectional data extracted from a longitudinal study.

AD = Alzheimer's disease; B12 = Vitamin B12; BDI-II = Beck Depression Inventory-II; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CVD = cardiovascular disease; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorder, fourth edition, text revision; ECT = electroconvulsive therapy; EEG = electroencephalography; ERT = estrogen replacement therapy; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HAMD = Hamilton Depression Rating Scale; ICD = International Classification of Diseases; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; MRI = magnetic resonance imaging; NIA-AA = National Institute on Aging and Alzheimer's Association; OCD = obsessive compulsive disorder; PD = Parkinson's disease; REM = eye movement; SMMSE = Standardized Mini-Mental Status Exam; TBI = traumatic brain injury; TIA = transient ischemic attack; TSH = thyroid stimulating hormone.

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