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Is the Impact of Somatic Diseases on Cognitive Functions Clinically Important?

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Abstract

Background/Objectives: Somatic multimorbidity and mental disorders are associated with impaired cognitive functions, but the clinical importance has rarely been considered. This study evaluated the clinical importance of the associations between cognitive functions and somatic comorbidity. **Methods**: This cross-sectional study used data from the national research and quality registry "The Norwegian Registry of Persons Assessed for Cognitive Symptoms" (NorCog). Out of 9525 persons in the registry, 3794 (males/females 1789 (47%)/2005 (53%) with a mean age of 74.8 (SD 8.6) years) with mild cognitive impairment (MCI) and dementia had complete registration of age, sex, BMI, years of education, depression (Cornell scale), and somatic diseases and were included in the study. Cognitive functions were assessed with a Norwegian version of Mini-Mental State Examination (MMSE-NR3), Word List Memory Test (WLMT) Immediate and Delayed recall, and Trail Making Test (TMT) A and B. Changes were compared with established limits for minimal clinically important differences (MCID). Twenty-six somatic disorders were registered and grouped into cardiovascular disease, cerebrovascular disease, neurological disease, and metabolic disease. All associations between cognitive functions and somatic diseases were studied using linear regression with the cognitive test scores as dependent variables and somatic diseases as predictors **Results**: The number of comorbidities and cerebrovascular disease was statistically significantly associated with improved MMSE-NR3 and WLMT Immediate and Delayed test scores. The changes in scores were not clinically important. Neurological disease was associated with improved WLMT Delayed scores and impaired TMT-A scores, but neither change was clinically important. **Conclusions**: There were statistically significant associations between somatic morbidity and cognitive functions, but none were clinically important. Referral to MCID in addition to statistical differences deserves increased attention in clinical studies.

Keywords: cognitive function; comorbidity; dementia; depression; minimal clinically important difference; multimorbidity; somatic diseases

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1. Introduction

Somatic multimorbidity, mental disorders, and reduced cognitive functions/dementia are common and associated disorders in older adults [1–4]. Multimorbidity affects more

than 80% of people with dementia and worsens the outcome [4]. Mental disorders (anxiety and depression) and somatic multimorbidity are associated with impaired cognitive function and dementia [5–7]. The interaction between the disorders deserves clinical attention because comorbidities may be misdiagnosed as symptoms of dementia, and dementia hampers the recognition of comorbidities [8,9]. Optimal treatment of somatic comorbidity and mental disorders has been shown to decrease the risk of hospitalization, reduce healthcare costs, improve physical performance and quality of life, and improve cognitive functions in persons with cognitive impairment [9]. Interventions for somatic disorders are important for patient well-being, but for a reduction in cognitive decline and/or dementia, the effects are uncertain. According to a recent review from the WHO, the certainty of evidence for reduced risk of cognitive decline and/or dementia by interventions for obesity, diabetes, hypertension, dyslipidemia, stroke, and traumatic brain injury has been graded from none to low to moderate [10].

Associations between comorbidity and cognitive function vary across studies because of differences in study design. However, for clinicians, the clinical importance of changes in cognitive function matters more than statistical differences. Most studies do not comment on clinical importance. Highly statistically significant associations in large studies may be clinically irrelevant [11,12].

This study used data from a national registry to study associations between somatic comorbidity and cognitive functions adjusted for known confounders [13]. The primary aim was to assess the clinical importance of changes in cognitive function.

2. Materials and Methods

2.1. Data Materials

This study used data from the national research and quality registry "The Norwegian Registry of Persons Assessed for Cognitive Symptoms" (NorCog) [13]. From 2009 to 2021, NorCog included 18,120 persons referred by general practitioners (GPs) to outpatient clinics and Norwegian specialist healthcare centers for the assessment of impaired cognitive function and suspected dementia. The ability to give informed consent was an inclusion criterion, and voluntary written informed consent was obtained before inclusion. In almost all cases, the person's legal representative participated in the assessment and provided information about the person's health status and the course of cognitive decline. Most often, both gave informed consent. All persons were living at home with mild and moderate cognitive impairment. Information about comorbidities was provided by the participant, their next of kin, and the patient records.

2.2. Methods

This cross-sectional study used data from participants' first clinic visits. Only participants with complete data on age, sex, body mass index (BMI), years of education, depression, and somatic diseases, and those diagnosed with mild cognitive impairment (MCI) or verified dementia diagnoses, were included. Persons with MCI and dementia were analyzed both as one group and separately.

MCI was defined according to the criteria of Winblad et al. [14]: The person is neither normal nor demented, but there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in relation to objective cognitive deficits. Activities of daily living are preserved.

The Dementia group included persons with Alzheimer's disease (AD), mixed AD/vascular dementia (MixADVD), vascular dementia (VD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB). The diagnostic criteria of FTD and DLB were according to Neary et al. [15] and McKeith et al. [16], respectively; other dementia diagnoses were

according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10).

2.3. Variables

2.3.1. Person Characteristics

- Sex (male/female); age (years); years of education; BMI (kg/m^2).
- Twenty-six somatic diseases registered as previous/present or no (yes/no): cerebral infarction, cerebral bleeding, Transient Ischemic Attack, Paresis, other cerebrovascular event, hypertension, Atrial fibrillation, heart failure, Angina pectoris, Myocardial infarction, other heart disease, Parkinson's disease, Epilepsia, Head injury, Encephalitis, other cerebral disease, Hypercholesterolemia, diabetes mellitus, obesity (BMI ≥ 30 kg/m^2), chronic obstructive pulmonary disease, Polyarthritis, cancer, Hypothyroidism, Vitamin B12 insufficiency, Renal disease, and other. Reported as number of somatic diseases: 0–26.
- Four disease groups:
    1. Cerebrovascular diseases: cerebral infarction, cerebral bleeding, Transient Ischemic Attack, Paresis, and other cerebrovascular events.
    2. Cardiovascular diseases: hypertension, Atrial fibrillation, heart failure, Angina pectoris, Myocardial infarction, and other heart diseases.
    3. Neurological diseases: Parkinson's disease, Epilepsy, Head injury, Encephalitis, and other cerebral diseases.
    4. Metabolic diseases: Hypercholesterolemia, diabetes mellitus, and obesity (BMI ≥ 30 kg/m^2).

2.3.2. Tests of Cognitive Functions

- Mini-Mental State Examination—NR3 (MMSE-NR3) is a validated Norwegian screening test of cognitive functions, with a score of 0–30 [17]. Better performance gives higher scores. Population-based reference score: 28.5 (SD 1.3) [18].
- Memory was tested with a demographically adjusted version of the Word List Memory Test (WLMT) in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [19–21]. High scores indicate better performance.
    - WLMT Immediate recall (WLMT-Imm): 10 words were repeated three times, and recall was tested after each presentation (score: 0–30); reference score 18.6 (SD 3.5) [21].
    - WLMT Delayed recall (WLMT-Delay) was the recall of 10 words after a delay of 10 min (score 1–10); reference score 5.8 (SD 1.7) [21].
- Trail Making Tests A and B (TMT-A and TMT-B) measure mental flexibility, tempo, attention, and executive functions [22,23]. A Norwegian manual, TMT-NR3, was used. Low scores indicate better performance.
    - TMT-A and TMT-B reference scores in a population with a mean age of 72.9 (SD 5.5) years are 46.4 (SD 17.6) and 104.0 (SD 51.8), respectively [24].
- Cornell scale. The scale is a measure of depressive symptoms in persons with cognitive impairment and dementia, with scores ranging from 0 to 38. Scores ≥12 indicate moderate to severe depression [25].

2.4. Statistics

Participants' characteristics are reported as means with SD and numbers with proportions (%). Exact chi-square test, *t*-test, and Mann–Whitney U test were used to compare participant characteristics between the MCI and Dementia groups. All the associations

between cognitive test scores and somatic comorbidity were analyzed using linear regression with the cognitive test scores as dependent variables and somatic comorbidities as predictors, adjusted for age, sex, BMI, years of education, Cornell score, and group (MCI/Dementia), and reported as unstandardized B-values with 95% CI and significance levels (p-values). Interaction analyses between comorbidity and group (MCI/Dementia) were added as needed.

To reduce type 1 errors in this study with multiple statistical testing, $p \leq 0.01$ was considered statistically significant. This reduction in the p-value is a pragmatic, not formal, correction to reduce type 1 errors in studies with multiple testing. Because statistically significant differences are not necessarily clinically significant, particularly in large datasets, the statistically significant results were compared with the Minimal Clinically Important Differences (MCID). A difference was judged clinically important if it was statistically significant and equal to or greater than the MCID. Associations between comorbidity and cognitive functions have been studied with both cross-sectional and longitudinal designs [1–3]. MCDI are commonly estimated and used for within-person comparisons. If the difference is clinically important in within-person comparisons, there is no reason to believe it is not clinically important in between-person comparisons. We are not aware of different MCID values for within- and between-person comparisons. The applied MCDI are the best available ones. Studies evaluating MCID separately for persons with MCI and dementia report approximately 30% higher values for dementia than for MCI. We, therefore, added 30% to the MCID for persons with dementia if separate MCID values for MCI and dementia were not available.

The following MCDI values with differences between the groups, MCI and Dementia, were used.

- For MMSE-NR3, the MCID values published by Muir et al. were used: MCI 1.5; Dementia 2.0 [26].
- Formal evaluations of the MCIDs for WLMT Immediate and Delayed recall do not exist. Therefore, the standard deviations in the study by Wagle et al. were used for MCI and increased by 30% for the Dementia group: MCID for WLMT Immediate: MCI 3.5; Dementia 4.6; and for WLMT delayed: MCI 1.7; Dementia 2.2 [21].
- For TMT-A and TMT-B, the MCID values for MCI published by Borland et al. were used: TMT-A 13.0; TMT-B 20.1. Thirty percent was added for Dementia: TMT-A 17.0; TMT-B 26.5 [24]

3. Results

Of 9525 persons in the NorCog datafile available for this study, 3794 persons (1789 (47%) males and 2005 (53%) females with a mean age of 74.8 (SD 8.6) years) had complete registration of age, sex, BMI, years of education, Cornell scale, and somatic diseases and were included in this study. Table 1 presents the characteristics of all participants and, separately, for the MCI and Dementia groups, with comparisons between the groups. Not all participants had completed the cognitive tests; the numbers indicate the completion rate for each test.

Table 2 presents the associations between cognitive test scores and age, sex, BMI, education, Cornell, group (MCI/Dementia), and number of comorbidities. MMSE-NR3 and WLMT Immediate and Delayed recall improved significantly with increasing number of comorbidities. Comorbidity was not significantly associated with either TMT test. Except for TMT-B, no significant interactions between group (MCI/Dementia) and comorbidity were observed, indicating that the associations between comorbidity and cognitive test scores did not differ significantly between the MCI and Dementia groups. TMT-B scores worsened significantly with increasing comorbidity in the MCI group but not in the Dementia group.

This difference between the groups was statistically significant ($p = 0.001$). Table 2 gives the details.

Table 1. Participants' characteristics.

Variables	Mean (SD), Number (%)			Statistics *p*-Values
	All (no 3794)	MCI (no 1592)	Dementia (no 2202)	MCI vs. Dementia
Age (years)	74.8 (8.6)	72.8 (9.1)	76.3 (7.9)	**$p < 0.001$**
Sex (male/female)	1789 (47%)/ 2005 (53%)	804 (51%)/ 788 (49%)	985 (45%)/ 1217 (55%)	**$p < 0.001$**
Years of education	11.2 (3.8)	11.6 (3.6)	10.8 (3.8)	**$p < 0.001$**
BMI (kg/m^2)	25.4 (4.5)	25.9 (4.5)	25.1 (4.4)	**$p < 0.001$**
Cornell [1]	6.4 (5.5)	5.7 (5.4)	6.8 (5.5)	**$p < 0.001$**
Number of somatic diseases	2.3 (SD 1.8) range 0–12	2.4 (1.8) range 0–12	2.2 (1.8) range 0–11	$p = 0.011$ *
Without somatic disease	644 (17.0%)	253 (16%)	391 (18%)	$p = 0.136$
Cardiovascular disease	2167 (57%)	916 (58%)	1251 (57%)	$p = 0.666$
only cardiovascular disease	392 (10.3%)	146 (9.2%)	246 (11.2%)	$p = 0.052$
Cerebrovascular disease	840 (22%)	362 (22.7%)	478 (21.7%)	$p = 0.452$
only cerebrovascular disease	71 (1.9%)	23 (1.4%)	48 (2.2%)	$p = 0.114$
Neurological disease	541 (14%)	258 (16%)	283 (13%)	**$p = 0.004$**
only neurological disease	89 (2.3%)	37 (2.3%)	52 (2.4%)	$p = 1.000$
Metabolic disease	1397 (37%)	621 (39%)	776 (35%)	$p = 0.019$
only metabolic disease	169 (4.5%)	79 (5.0%)	90 (4.1%)	$p = 0.203$
MMSE-NR3 [2] (no 2948)	22.7 (4.5)	24.9 (3.6)	20.9 (4.4)	**$p < 0.001$ ***
WLMT Imm [3] (no 3217)	11.4 (4.7)	13.4 (4.5)	9.8 (4.3)	**$p < 0.001$ ***
WLMT Delay [4] (no 3198)	1.9 (2.1)	2.8 (2.3)	1.2 (1.6)	**$p < 0.001$ ***
TMT-A [5] (no 3456)	92 (65)	73 (46)	108 (73)	**$p < 0.001$ ***
TMT-B [6] (no 1757)	196 (103)	183 (102)	215 (102)	**$p < 0.001$ ***

Statistically significant *p*-values in bold face. * Mann–Whitney U Test. [1] Cornell: Cornell depression scale. [2] MMSE-NR3: Mini-Mental State Examination—Norwegian version 3. [3,4] WLMT: Word List Memory Test Immediate and Delayed. [5,6] TMT: Trail Making Test A and B.

Table 2. This table presents the associations between cognitive test scores (MMSE-NR3, WLMT Immediate and Delayed recall, and TMT A and B) and the number of comorbidities (0–26). Linear regression analyses were adjusted for age, sex, BMI, years of education, Cornell score, and the groups dementia/MCI and reported as unstandardized B-values with 95% CI and significance levels.

Dependent Variable	Age (Years)	Sex (Male)	BMI (kg/m^2)	Education (Years)	Cornell [1]	Dementia vs. MCI	Comorbidity (Number)
MMSE-NR3 [2]	−0.05 (−0.07; −0.03) **$p < 0.001$**	0.44 (0.15; 0.73) **$p = 0.003$**	0.05 (0.01; 0.08) **$p = 0.007$**	0.23 (0.19; 0.27) **$p < 0.001$**	0.01 (−0.02; 0.04) $p = 0.490$	−3.62 (−3.91; −3.32) **$p < 0.001$**	0.15 (0.06; 0.24) **$p < 0.001$**
						* 0.05 (−0.11; 0.21), $p = 0.562$	
WLMT Immediate [3]	−0.10 (−0.12; −0.08) **$p < 0.001$**	−0.51 (−0.81; −0.21) **$p < 0.001$**	0.05 (0.02; 0.09) **$p = 0.003$**	0.20 (0.16; 0.24) **$p < 0.001$**	0.03 (0.00; 0.06) $p = 0.025$	−3.09 (−3.39; −2.79) **$p < 0.001$**	0.13 (0.04; 0.22) **$p = 0.003$**
						* −0.02 (−0.18; 0.15), $p = 0.852$	
WLMT Delayed [4]	−0.056 (−0.06; −0.05) **$p < 0.001$**	−0.01 (−0.14; 0.13) $p = 0.925$	0.03 (0.01; 0.04) **$p = 0.001$**	0.06 (0.04; 0.08) **$p < 0.001$**	0.03 (0.02; 0.04) **$p < 0.001$**	−1.32 (−1.46; −1.19) **$p < 0.001$**	0.07 (0.03; 0.11) **$p < 0.001$**
						* 0.00 (−0.07; 0.07), $p = 0.983$	

Table 2. *Cont*.

Dependent Variable	Age (Years)	Sex (Male)	BMI (kg/m^2)	Education (Years)	Cornell [1]	Dementia vs. MCI	Comorbidity (Number)
TMT-A [5]	1.10 (0.84; 1.35)	12.8 (8.6; 17.0)	−0.61 (−1.09; −0.12)	−1.99 (−2.59; −1.39)	0.48 (0.10; 0.86)	29.3 (25.0; 33.5)	0.54 (−0.69; 1.77)
	$p < 0.001$	**$p < 0.001$**	$p = 0.014$	**$p < 0.001$**	$p = 0.014$	**$p < 0.001$**	$p = 0.389$
						* −0.54 (−2.84; 1.75), $p = 0.643$	
TMT-B [6]	3.01 (2.48; 3.54)	12.3 (3.1; 21.4)	−0.62 (−1.70; 0.47)	−5.53 (−6.79; −4.26)	0.85 (−0.03; 1.73)	21.0 (11.7; 30.3)	2.72 (0.02; 5.41)
	$p < 0.001$	**$p = 0.009$**	$p = 0.268$	**$p < 0.001$**	$p = 0.058$	**$p < 0.001$**	$p = 0.048$
						* −8.66 (−13.84; −3.48), **$p = 0.001$**	

Statistically significant *p*-values in bold face. [1] Cornell: Cornell depression scale. [2] MMSE-NR3: Mini-Mental State Examination—Norwegian version 3. [3,4] WLMT: Word List Memory Test Immediate and Delayed. [5,6] TMT: Trail Making Test A and B. * Interaction: Comorbidity*Group (MCI/Dementia). The associations between TMT-B and comorbidity in the MCI and Dementia groups were B: 5.91 (95% CI 2.61; 9.20), $p < 0.001$, and B: −2.75 (95% CI −6.99; 1.48), $p = 0.203$, respectively.

Table 3 compares cognitive test scores between persons with cerebrovascular disease, cardiovascular disease, neurological disease, and metabolic disease with those without any somatic disease. Cognitive performance, as measured by MMSE-NR3 and WLMT Immediate and Delayed, was significantly better in persons with cerebrovascular disease than in those without. In those with neurological disease, WLMT Delayed improved significantly, whereas TMT-A deteriorated. Table 3 gives the details.

Table 3. This table presents differences in cognitive test scores (MMSE-NR3, WLMT Immediate and Delayed, and TMT-A and B) between persons with cerebrovascular disease, cardiovascular disease, neurological disease, or metabolic disease, regardless of additional somatic diseases, and those without any somatic disease. References to the MCID values are given. Analyzed with a linear regression model adjusted for age, sex, BMI, years of education, Cornell score, and group (MCI/Dementia) and given as differences between the means with 95% CI and *p*-values.

Dependent Variable	Diseases D vs. H Diff [1] (95% CI); *p*-Value			
	Cerebrovascular Disease	Cardiovascular Disease	Neurological Disease	Metabolic Disease
MMSE-NR3 [3]	0.95 (0.45; 1.44)	0.52 (0.10; 0.93)	0.63 (0.08; 1.18)	0.59 (0.13; 1.04)
(MCID: 1.5; 2.0) [2]	**$p < 0.001$**	$p = 0.015$	$p = 0.024$	$p = 0.011$
WLMT Imm [4]	0.68 (0.19; 1.18)	0.44 (0.01; 0.86)	0.60 (0.03; 1.17)	0.46 (−0.13; 0.94)
(MCID: 3.5; 4.6) [2]	**$p = 0.007$**	$p = 0.044$	$p = 0.039$	$p = 0.057$
WLMT Delay [5]	0.41 (0.20; 0.63)	0.11 (−0.08; 0.29)	0.34 (0.09; 0.58)	0.07 (−0.14; 0.28)
(MCID: 1.7; 2.2) [2]	**$p < 0.001$**	$p = 0.257$	**$p = 0.007$**	$p = 0.504$
TMT-A [6]	1.37 (−5.58; 8.32)	0.56 (−5.66; 6.76)	10.74 (2.90; 18.57)	−3.41 (−9.81; 3.00)
(MCID: 13.0; 17.0) [2]	$p = 0.699$	$p = 0.860$	**$p = 0.007$**	$p = 0.297$
TMT-B [7]	11.33 (−4.45; 27.10)	4.79 (−8.62; 18.01)	8.19 (−8.17; 24.54)	1.09 (−13.04; 15.21)
(MCID: 20.1; 26.5) [2]	$p = 0.159$	$p = 0.489$	$p = 0.326$	$p = 0.880$

Statistically significant *p*-values in bold face. [1] D vs. H Diff: Difference between those with and without the disease. [2] MCID: Minimal Clinically Important Difference in the groups MCI and Dementia. [3] MMSE-NR3: Mini-Mental State Examination—Norwegian version 3. [4,5] WLMT: Word List Memory Test Immediate and Delayed. [6,7] TMT: Trail Making Test A and B. There were no significant interactions between the diseases and group (MCI/Dementia).

To study the net effect of each somatic disease on cognitive functions, differences in cognitive test scores between persons with only a single somatic disease and those without any somatic disease were analyzed. There were no statistically significant differences

between those with and without disease and no significant interactions between those with disease and the groups (MCI/Dementia). Table 4 presents the details.

Table 4. This table compares cognitive test scores in persons with one of four somatic diseases (cerebrovascular disease, cardiovascular disease, neurological disease, and metabolic disease) without any other somatic diseases, with those without any somatic disease. References to the MCID values are given. Analyzed with a linear regression model adjusted for age, sex, BMI, years of education, Cornell score, and group (MCI/Dementia), and reported as unstandardized B-values with 95% CI.

Dependent Variable	Diseases D vs. H Diff [1] (95% CI); *p*-Value			
	Cerebrovascular Disease	**Cardiovascular Disease**	**Neurological Disease**	**Metabolic Disease**
MMSE-NR3 [3] (MCID: 1.5; 2.0) [2]	1.02 (−0.16; 2.20) $p = 0.089$	0.40 (−0.21; 1.01) $p = 0.202$	0.28 (−0.78; 1.34) $p = 0.604$	0.39 (−0.47; 1.26) $p = 0.371$
WLMT Imm [4] (MCID: 3.5; 4.6) [2]	0.01 (−1.06; 1.08) $p = 0.989$	−0.02 (−0.61; 0.57) $p = 0.949$	0.46 (−0.59; 1.52) $p = 0.391$	0.26 (−0.62; 1.14) $p = 0.562$
WLMT Delay [5] (MCID: 1.7; 2.2) [2]	0.46 (0.01; 0.97) $p = 0.046$	−0.13 (−0.37; 0.11) $p = 0.299$	0.01 (−0.43; 0.44) $p = 0.979$	−0.29 (−0.65; 0.06) $p = 0.120$
TMT-A [6] (MCID: 13.0; 17.0) [2]	4.82 (−11.18; 20.82) $p = 0.554$	0.08 (−8.65; 8.80) $p = 0.986$	12.9 (−2.06; 27.70) $p = 0.093$	−5.32 (−16.41; 5.77) $p = 0.347$
TMT-B [7] (MCID: 20.1; 26.5) [2]	16.05 (−20.19; 52.29) $p = 0.384$	0.88 (−17.4; 19.1) $p = 0.925$	15.8 (−16.9; 48.5) $p = 0.343$	−9.34 (−34.0; 15.3) $p = 0.457$

[1] D vs. H: Diseased versus Healthy. [2] MCID: Minimal Clinically Important Difference in the groups MCI and Dementia. [3] MMSE-NR3: Mini-Mental State Examination—Norwegian version 3. [4,5] WLMT: Word List Memory Test Immediate and Delayed. [6,7] TMT: Trail Making Test A and B. No significant interactions were observed between disease and group (MCI/Dementia).

4. Discussion

4.1. Multiple Comorbidities and Cognitive Test Scores

In this cross-sectional study, MMSE-NR3, WLMT Immediate, and WLMT Delayed test scores improved significantly with increasing somatic comorbidity. Although the associations between multimorbidity and improved test results were statistically significant, they were likely to be clinically unimportant. Even with 10–12 comorbidities, the difference between those without any comorbidity is on the lower limit of the MCID for MMSE-NR3 and below the MCID limits for the WLMT tests.

The improvement in test scores with increasing comorbidity was unexpected since studies have shown significant associations between multimorbidity and dementia [1,2]. Similarly, the MCI group had somewhat more comorbidities and significantly better cognitive test scores than the Dementia group. In a recently published meta-analysis including cross-sectional studies, the risk of prodromal stages of dementia was significantly higher in persons aged > 65 years (the same age subgroup as this study) with two or more comorbidities than in those with zero or one (OR 1.33) [1]. A similar clear association between dementia and multimorbidity was reported in a Spanish cross-sectional study of more than 72,000 patients aged 65 or older [2]. The association between multimorbidity and an increased risk of dementia has been even better documented in meta-analyses of longitudinal cohort studies [1,3]. These studies did not report results on cognitive tests, but people with a diagnosis of MCI and dementia probably have poorer results on cognitive tests. Thus, we can compare our results with the studies mentioned above. However, these studies did not address the clinical importance of the associations with cognitive function.

The reasons for the unexpected finding of better cognitive test scores among individuals with more comorbidities are unclear. The study population appears similar to that of other studies. Age, sex, and the number of somatic morbidities were in the same range as those of other studies referred to. Several factors may explain the differences.

First, people with somatic diseases often visit general practitioners and are well known to them. Cognitive deficits are, therefore, detected early in the disease, and the patients are referred for assessment. Persons without somatic comorbidity do not visit GPs until they or their next of kin suspect cognitive deficits (i.e., a later stage of the disease). Thus, in the studied population, cognitive function may be better in persons with somatic diseases than in those without. Norway's primary care organization, where each person is assigned a specific GP responsible for follow-up, might enhance this effect.

Second, it is likely that GPs' referrals to specialist healthcare centers for the assessment of cognitive deficits and suspected dementia are independent of the person's somatic morbidity and degree of cognitive deficits. Symptoms commonly associated with somatic morbidity and cognitive impairment, such as sleep disturbances, sleepiness, asthenia, anxiety, depression, and side effects of (poly)pharmacy, might be misinterpreted as cognitive impairment [4,5]. Therefore, cognitive testing of persons with seemingly similar cognitive function might yield better results in those with somatic comorbidity than in those without, because symptoms may be misattributed to cognitive impairment.

Third, defining multimorbidity and adjusting for confounders are prerequisites for accurately estimating the effect of somatic comorbidity on cognitive functions. Zhou et al.'s meta-analysis of longitudinal cohort studies specifies the definition of comorbidity for each included study [3]. Some of the studies included mental health (neuro-psychiatric diseases, anxiety, and depression) in the morbidity group; others did not. Cognitive functions depend on age, sex, education, anxiety, depression, and, to some degree, BMI [4,5,27]. According to the meta-analysis by Xin et al. [1], most studies adjusted for age, sex, and education. Depression, which is strongly associated with both somatic diseases and cognitive impairment and dementia [6,7], was not mentioned. Typical symptoms of depression, such as lack of concentration and indecision, are also symptoms of dementia. Estimating the association between somatic comorbidity and cognitive functions without information about the diseases included in the term 'comorbidity' and the variables adjusted for yields imprecise results. These factors could explain the discrepancies between our study and other studies. Our study focused on the associations between somatic morbidity and cognitive functions adjusted for depression in addition to age, sex, BMI, and education.

Fourth, survival bias and resilience factors are hypothetical and undocumented explanations for the unexpected result. Older adults who have survived with somatic comorbidity might have resilience factors protecting them from or delaying the onset of dementia. Associations between somatic morbidity and cognitive impairment could, therefore, differ between older adults with resilience factors and people with fewer resilience factors who may have died earlier in life.

A fifth explanation may relate to the study design. The present study had a cross-sectional design, registering the present and not the duration of comorbidities. Longstanding somatic diseases may be associated with a higher risk of cognitive impairment than short-standing diseases, and the risk may vary across diseases.

Our study included only somatic comorbidity in the comorbidity term and adjusted for age, sex, BMI, education, and depression. In addition, socioeconomic status, access to healthcare, health behaviors, loneliness, and stress are factors not included in either our study or in most other studies [4].

As expected, because the diagnoses were based on clinical evaluations, all cognitive test scores were significantly impaired in the Dementia group compared with the MCI group, in both the unadjusted (Table 1) and adjusted analyses (Table 2). However, the associations between somatic comorbidity and the test scores did not differ between the MCI and Dementia groups, except for TMT-B. The significant deleterious association between comorbidity and TMT-B in the MCI group, but not in the Dementia group, may reflect a low

completion rate among those with severe cognitive impairment and multiple comorbidities and the expected weak results in the Dementia group. TMT-B is a complex and challenging test that most people with dementia struggle with. Another explanation is that some patients with dementia were misdiagnosed as having MCI. Misdiagnosis could occur if the diagnosis of MCI is based only on cognition without considering functional impairment.

4.2. Specific Comorbidities and Cognitive Test Scores

The associations between multimorbidity and cognitive tests differ across single comorbidities, depend on interactions among them, and vary by comorbidity profile [8]. In this study, comorbidities were classified into four groups. Cerebrovascular disease was significantly associated with improved MMSE-NR3, WLMT Immediate, and WLMT Delayed scores, whereas neurological disease was associated with improved WLMT Delayed recall and impaired TMT-A scores. Possible explanations for improved cognitive test results in persons with cerebrovascular and neurological diseases are the same as those mentioned for comorbidity. Cognitive function did not differ significantly between persons with one of four somatic disease groups without other somatic diseases and those without having any somatic disease. The associations were independent of the group (MCI/Dementia). None of the differences between those without and with diseases, nor the disease alone or in combination with other diseases, were of clinical importance. The expected reduced cognitive functions in persons with cerebrovascular disease were not observed.

Other studies report various associations between specific comorbidities and dementia. In the study by Poblador-Plou et al. [2], Parkinson's disease, congestive heart failure, cerebrovascular disease, anemia, cardiac arrhythmia, chronic skin ulcers, osteoporosis, thyroid disease, retinal disorders, prostatic hypertrophy, insomnia, and anxiety were significantly associated with dementia. Zhou et al. [3] studied specific somatic diseases individually and reported their combinations. The combination of diabetes, heart disease, and stroke had the strongest association with dementia. Two reviews report that cardiovascular diseases and cardiovascular–metabolic conditions have the highest prevalence of dementia without mentioning the clinical importance [1,28].

4.3. Other Variables and Cognitive Test Scores

Adjusting for confounders is mandatory in studying associations between cognitive functions and somatic comorbidity. In this study, age, sex, and education, as in most studies, were statistically significantly associated with the cognitive tests [5]. The association between BMI and dementia is controversial [27,29]. In this study, high BMI was associated with better MMSE-NR3 and WLMT scores. It has been hypothesized that a high BMI in midlife increases the risk of dementia, especially if combined with a decline in subsequent years [27,29]. Depression is associated with dementia, but the relationship is unclear [5,6]. In this study, the association was not clinically important. Depression might be a prodromal symptom of dementia, and because of the overlap in symptoms between the diseases, depression remains unrecognized in persons with dementia [6]. The high prevalence of depressive disorders in persons with somatic multimorbidity makes it even more important to adjust for depression in studying associations between somatic comorbidity and cognitive functions [7].

4.4. Minimal Clinically Important Differences (MCID)

Statistically significant differences do not necessarily imply clinically meaningful differences. The distinction between minimally detectable differences and clinically important differences has implications for clinical practice [12]. The MCID is the smallest meaningful change for patients and healthcare providers. Determining the MCIDs raises method-

ological concerns [11,30]. This study used MCID values established in other studies and defined a clinically important difference as one that exceeded the MCID and was statistically significant. Multiple significant associations between somatic comorbidity and cognitive functions were below the MCID. In this study, somatic comorbidity was not judged clinically important for cognitive function according to the MCID limits used. This is in accordance with the WHO guidelines that the certainty of evidence is low for a risk-reducing effects on cognitive decline and/or dementia by reducing somatic morbidity [10]. If clinical studies include the MCID, many disagreements between studies will likely disappear. This does not mean that identifying somatic diseases is unimportant. Treatment of somatic diseases reduces the risk of hospitalization and costs and improves physical activity and quality of life in persons with dementia [9].

4.5. Strengths and Limitations

Persons referred by GPs for evaluation of cognitive functions were an unselected group, and nearly all provided informed consent. Those with the diagnosis of MCI and Dementia were included in this study. The diagnoses were based on a combination of diagnostic criteria and clinical judgement. The large number of clinics, with some variations among them, might have reduced the reliability of the diagnoses. However, there were annual seminars and monthly video meetings, with discussions of methods and diagnoses to improve data reliability. Selection bias due to incomplete registration was a limitation; only 40% had complete registration of age, sex, BMI, years of education, the Cornell scale, and somatic diseases, and were included in the analyses. Additionally, many participants dropped out of the cognitive tests. The lowest participation rate was in the TMT-B, probably the most demanding test for people with dementia. The high dropout rate may have introduced attrition bias, which was somewhat reduced by adjusting the analyses for sex, age, etc. But, even in this group, the number was substantial. It is likely that the dropout rate was highest in those with advanced cognitive impairment. Information on comorbidity was obtained from the participant, their next of kin, and the medical records, rather than entirely from medical records, which are more reliable [3]. One important strength of this study was the reporting of the clinical importance of the findings (MCID) and not only statistical differences. The MCID values used might also be an important limitation of this study. The MCID thresholds are derived from other contexts. The thresholds have mostly been established for within-person changes but are likely valid for between-person changes as well, as used in this study. The MCID values have not been directly established for dementia populations either, and some of the values have been extrapolated, including applying a 30% increase for dementia.

Excluding mental and neuropsychiatric comorbidities and studying only somatic comorbidity may have underestimated the overall effect of comorbidity on cognition. Adjusting for depression, which might be interpreted as cognitive impairment, is a strength.

4.6. Conclusions

The main finding of the present study was that in a population with MCI and dementia, there were statistically significant, but not clinically important, associations between somatic comorbidity and cognitive function. However, this study does not exclude clinically important associations because some confidence intervals were wide, referral bias might have occurred, and incomplete data may have introduced selection bias. Referral to MCID in addition to statistical results deserves increased attention in clinical studies.

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Informed Consent Statement: Informed consent was obtained from all persons involved in the study.

Data Availability Statement: The national registry NorCog is responsible for the source data. The de-identified data files were transferred to Innlandet Hospital Trust Brumunddal, Norway, and stored on a dedicated research server. The security follows the rules given by The Norwegian Data Protection Authority, P.O. Box 8177 Dep. NO-0034 Oslo, Norway. The data are available upon request to the author.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's Disease
BMI	Body Mass Index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
DLB	Dementia with Lewy bodies
FTD	Frontotemporal Dementia.
GP	General Practitioner
ICD10	International Statistical Classification of Diseases and Related Health Problems-10th revision
MCI	Mild cognitive impairment
MCID	Minimal Clinically Important Difference
MMSE-NR3	Mini-Mental State Examination—Norwegian version 3
NorCog	The Norwegian Registry of Persons Assessed for Cognitive Symptoms
SD	Standard deviation
TMT-A	Trail Making Test A
TMT-B	Trail Making Test B
VD	Vascular Dementia
WLMT Delay	World List Memory Test—Delayed recall
WLMT Imm	World List Memory Test—Immediate recall

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