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Association between comorbidity indices and nursing home admission in patients with Alzheimer's disease: a longitudinal observational study using the MEMORA cohort

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Abstract

Background Alzheimer's disease (AD) is among the leading cause of nursing home admission (NHA). Identifying potentially modifiable factors associated with the risk of NHA is crucial to reduce this risk in individuals with AD.

Objective We aimed to assess the relationship between comorbidity burden, as measured by the Charlson comorbidity index, the multimorbidity-weighted index and the health related quality of life comorbidity index, and NHA in patients with AD.

Methods We conducted an observational longitudinal study including patients from the MEMORA real-life cohort. Patients had to be aged 60 years or older, with a diagnosis of AD. The association between comorbidity indices and occurrence of NHA was assessed using Cox proportional-hazards models and competing-risks regressions considering mortality as a competing event. All analyses were adjusted for age, sex, educational level, stage of AD and the presence of neuropsychiatric symptoms.

Results Overall, 488 AD patients were included (68.2% with dementia). There were 125 (26%) NHA that occurred during the follow-up, with a median time of 25 months until NHA. Higher level of comorbidity burden as measured by the three comorbidity indices was associated with higher risk of NHA compared to lower level of comorbidity burden. Similar findings were found after considering mortality as a competing event, with a HR of 2.41(95%CI:1.36–4.28, $p=0.003$) for MWI, an HR of 1.96(95%CI:1.22–3.17, $p=0.006$), and an HR of 1.68(95%CI:1.04–2.71, $p=0.034$).

Conclusion The implementation of appropriate interventions that aim to improve the management of the comorbidity burden could help to reduce the risk of NHA in individuals with AD.

Keywords Comorbidity burden, Comorbidity index, Dementia, Alzheimer's disease, Nursing home

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease worldwide [1], and it is among the leading cause of nursing home admission (NHA) [1, 2]. The decline in cognitive performances and functional abilities was associated with higher risk of NHA in individuals with AD [3, 4].

Higher comorbidity burden as measured by comorbidity indices (for example the general medical health rating [5], the cumulative illness rating scale for geriatrics [6], and the Charlson comorbidity index [CCI] [7]) was associated with cognitive and functional autonomy decline in individuals with AD [5–7]. Therefore, higher comorbidity burden may contribute to an increase in the risk of NHA in individuals with AD. In this context, previous studies reported that some specific comorbidities such as urinary incontinence [8], depression [8], anxiety [9], psychosis [10] and heart disease [10] were significant predictors of NHA in individuals with AD [8–10]. In contrast, few studies that have examined the relationship between comorbidity indices and NHA in individuals with neurocognitive disorders (NCD), did not report a significant association [11, 12]. Thus, there is a lack of information regarding the association between comorbidity indices and NHA in individuals with AD.

Comorbidity indices consider both the number and severity of comorbidities [13], which allows us to understand whether global comorbidity burden has an impact on NHA in individuals with AD. Nevertheless, the lack of significant association when using comorbidity indices to predict NHA in individuals with NCD, may be related to the heterogeneity of this population regarding the underlying etiology (AD, vascular dementia, dementia with Lewy bodies and other unspecified dementia) [11, 12]. However, the prevalence of comorbidities [14–16], the number of comorbidities [15], and the comorbidity burden as measured by comorbidity indices [16, 17], were found to vary according to the etiology of NCD [14–17]. Moreover, the risk of NHA does not appear to be similar in AD and other NCD [2]. As consequence, confounding AD with other NCD may influence the assessment of the comorbidity burden as measured by comorbidity indices, as well as the association between comorbidity indices and NHA.

In this study, we aimed to assess the relationship between comorbidity burden, as measured by the CCI, the multimorbidity-weighted index and the health related quality of life comorbidity index, and NHA in patients with AD.

Methods

Study design and setting

We conducted an observational longitudinal study including patients from the MEMORA real-life cohort [18]. The MEMORA study included outpatients attending a memory consultation that had been conducted in the clinical and research memory center of Lyon. The MEMORA cohort was linked with the claim database from the regional French Primary Health Insurance Fund. Information was individually provided to the patients and caregivers at inclusion and oral consent was obtained. The MEMORA cohort protocol (clinicaltrial.gov number NCT02302482) has been approved by the regional ethics committee (Comité de protection des personnes Sud Est III) on July 29, 2014. Data processing has been approved by the national data protection commission.

Study population

The patients included in the present study were required to be aged 60 years or older, with a diagnosis of mild cognitive impairment (MCI) or dementia due to probable AD. AD diagnosis and the stage of cognitive impairment (MCI or dementia) were based on the medical evaluation of specialized physicians (geriatrician or neurologist or psychiatrist), without the systematic use of pathophysiological biomarkers [19, 20]. MCI and dementia stages were identified using the Diagnosis and Statistical Manual of mental disorders (DSM-V) [19–21]. We excluded patients with Mixed dementia (AD and cerebrovascular disease). All patients had to attend at least two visits at the Memory center, with a minimum follow-up of six months. This study included outpatients recruited between 2014 and 2019.

Outcome

The occurrence and date of first NHA were identified using the claim database. For patients who experienced NHA, the time until NHA was defined as the time in months between their first visit in the memory center and the date of NHA. For patients who did not experience NHA, the length of follow-up was censored at maximum 60 months or at the date of death. Date of death was provided through the claim database.

Comorbidity burden assessment

Comorbidities were gathered at the first visit in the memory center by specialized physicians. Comorbidities were reported by patient, caregiver (if present) and through the letter of patients' general practitioner. However, the information concerning the date of comorbidities' onset was not systematically collected.

We used three comorbidity indices to measure the comorbidity burden at baseline: the CCI, the multimorbidity-weighted index (MWI) and the health related quality of life comorbidity index (HRQOL-CI). These three indices were computed by identifying specific comorbidities and summing weights attributed to each comorbidity (additional file1) [22–24]. For the CCI the weights

of comorbidities were based on their associations with 1-year mortality prediction in hospitalized patients [22], for MWI the weights of comorbidities were based on their association with short form-36 physical functioning [23, 25], and for the HRQOL-CI the weights of comorbidities were based on their association with the short form-12 physical component summary [24]. Dementia or AD were not considered to calculate the three comorbidity indices as they correspond to the primary condition of included patients.

Comorbidity indices were also stratified into quartiles to create four levels of comorbidity burden, allowing for an assessment of their impact on NHA.

Sociodemographic characteristics, cognitive performances and functional autonomy

The sociodemographic characteristics considered in this study were age (under 80 years and 80 years), sex (female/male), educational level (till/ primary/secondary/tertiary), and the stage of AD (MCI/dementia), gathered at the first visit. The functional autonomy level was assessed by the Lawton instrumental activities of daily living scale (IADL) [26]. The neuropsychiatric symptoms were assessed by the neuropsychiatric inventory (NPI) [27]. Both questionnaires were administered to patients by specialized physiacians or trained nurses.

Statistical analyses

The baseline characteristics of patients were reported and compared according to the occurrence of NHA using the Pearson's chi-square test or the student's t-test, as appropriate. We performed Cox proportional-hazards models to calculate hazard ratios (HR) and 95% confidence intervals (95%CI) for: CCI, MWI, and HRQOL-CI as continuous variables, and for CCI, MWI, and HRQOL-CI as categorical variables. We performed competing-risks regression models with mortality as a competing event to calculate subdistribution hazard ratios (SHR) and 95%CI (Fine and Gray's method [28]) for: CCI, MWI and HRQOL-CI as continuous variables and for CCI, MWI, and HRQOL-CI as categorical variables. All models were adjusted for age, sex, educational level and stage of AD (MCI/dementia) at baseline. Since the NPI was not available for all patients, we conducted additional analyses to adjust models for NPI when available. The assumption of proportionality was verified by the Schoenfeld residuals of the variables included in the models. The predictive performance of Cox models was assessed by the C-index value. Population attributable fraction (PAF) for cohort studies was estimated using direct method to evaluate the fraction of NHA attributable to comorbidity indices as categorical variables (the used function was PAF_calc_discrete). Adjusted PAF (adjusted for age, sex, educational level and stage of AD [MCI/dementia]) was reported with 95%CI. All analyses were performed using R software (R.4.4.0; Lyon1, France). A p-value < 0.05 was considered as statistically significant.

Results

Baseline characteristics of study population

Overall, 488 AD patients were included in the study. The majority of patients were 80 years or older ($n = 318$, 65.2%) with a female predominance ($n = 334$, 68.4%). The most frequent education levels were the primary level ($n = 171$, 35%) and the secondary level ($n = 151$, 30.9%). There were more patients at dementia stage than MCI (68.2% vs. 31.8%), and the averages of IADL and NPI in the entire sample were 3.61 ± 2.21 and 21.6 ± 1.97, respectively (Table 1).

There were 125 (25.6%) NHA that occurred during the follow-up, with a median time of 25 months until NHA. During the follow-up, 37 (7.6%) patients had died, before NHA. The mean of MWI at baseline was higher in patients admitted in nursing home compared to patients not admitted in nursing home (7.56 ± 5.75 vs. 6.14 ± 4.99, $p = 0.015$). The mean of HRQOL-CI at baseline was higher in patients admitted in nursing home compared to patients not admitted in nursing home (3.43 ± 2.56 vs. 2.86 ± 2.43, $p = 0.030$). The mean of CCI was not significantly different according to NHA status (1.71 ± 1.56 vs. 1.50 ± 1.66, $p = 0.19$; Table 1).

Association between comorbidity indices and NHA in AD

When considering comorbidity indices as continuous variables, MWI and HRQOL-CI were significant predictors of NHA with a HR of 1.05 (95%CI [1.01;1.08]) and 1.12 (95%CI [1.04; 1.20]), respectively (Table 2; additional file 3). In contrast, CCI as continuous was not a significant predictor of NHA with a HR of 1.09 (95%CI [0.97;1.22]). When considering comorbidity indices as categorical variables, higher level of comorbidity burden as measured by CCI, MWI and HRQOL-CI presented a greater risk of NHA compared to lower level of comorbidity burden. The six models had similar performances according to the C-index value (61.3 to 63.3%; additional file 3). Over a 60 months period, the PAF associated with the MWI varied between 16.9 and 45.3%, the PAF associated with the HRQOL-CI varied between 9.05 and 31.1%, and the PAF associated with the CCI varied between 9 and 17.4% (additional file 2).

According to the competing-risks regression models (Table 2; additional file 4), MWI and HRQOL-CI, both as continuous remained significant predictors of NHA with SHR of 1.04 (95%CI [1.01; 1.08]) and 1.12 (95%CI [1.04; 1.20]), respectively. In contrast, the CCI as continuous was not a significant predictor of NHA. When considering comorbidity indices as categorical variables, higher level of comorbidity burden as measured by CCI, MWI

Table 1 Baseline characteristics of the study sample (*N* = 488)

Characteristics	Total (*N* = 488)	NHA		*p*
		Yes (*n* = 125, 25.6%)	No (*n* = 363, 74.4%)	
Age, year, mean ± SD	80.82 ± 7.04	82.34 ± 5.80	80.29 ± 7.36	0.002
Age category, n (%)				0.029
< 80 years	170 (34.8)	33 (19.4)	137 (80.6)	
≥ 80 years	318 (65.2)	92 (28.9)	226 (71.1)	
Sex/Gender, n (%)				0.98
Female	334 (68.4)	85 (25.4)	249 (74.6)	
Male	154 (31.6)	40 (26.0)	114 (74.0)	
Education level, n (%)				0.18
Till	92 (18.9)	28 (30.4)	64 (69.6)	
Primary	171 (35)	47 (27.5)	124 (72.5)	
Secondary	151 (30.9)	38 (25.2)	113 (74.8)	
Tertiary	74 (15.2)	12 (16.2)	62 (83.8)	
Stage of AD, n (%)				0.06
Dementia	333 (68.2)	94 (28.2)	239 (71.8)	
MCI	155 (31.8)	31 (20.0)	124 (80.0)	
IADL, mean ± SD	3.61 ± 2.21	3.31 ± 1.96	3.72 ± 2.29	0.06
Missing data (%)	20 (4.1)	0 (0)	20 (100)	
NPI, mean ± SD	21.6 ± 1.97	21.38 ± 15.38	21.71 ± 17.52	0.84
Missing data (%)	36 (7.4)	5 (13.9)	31 (86.1)	
CCI, mean ± SD	1.55 ± 1.64	1.71 ± 1.56	1.50 ± 1.66	0.19
CCI, median (IQR)	1 (0–2)	1 (0–3)	1 (0–2)	
CCI category, n (%)				0.026
0	164 (33.6)	36 (22.0)	128 (78.0)	
1	117 (24)	31 (26.5)	86 (73.5)	
2	91 (18.6)	17 (18.7)	74 (81.3)	
≥ 3	116 (23.8)	41 (35.3)	75 (64.7)	
MWI, mean ± SD	6.50 ± 5.23	7.56 ± 5.75	6.14 ± 4.99	0.015
MWI, median (IQR)	5.27 (2.23–9.60)	6.34 (3.16–10.48)	4.87 (1.87–9.27)	
MWI category, n (%)				
[0–2.23]	123 (25.2)	21 (17.1)	102 (82.9)	0.048
]2.23–5.27]	124 (25.4)	31 (25.0)	93 (75.0)	
]5.27–9.60]	119 (24.4)	34 (28.6)	85 (71.4)	
> 9.60	122 (25.0)	39 (32.0)	83 (68.0)	
HRQOL-CI, mean ± SD	3.01 ± 2.47	3.43 ± 2.56	2.86 ± 2.43	0.030
HRQOL-CI, median (IQR)	3 (1–4)	3 (1–5)	3 (1–4)	
HRQOL-CI category, n (%)				0.21
[0–1]	165 (33.8)	35 (21.2)	130 (78.8)	
[2–3]	149 (30.5)	38 (25.5)	111 (74.5)	
4	53 (10.9)	13 (24.5)	40 (75.5)	
≥ 5	121 (24.8)	39 (32.2)	82 (67.8)	
Follow-up, month, mean ± SD	24.93 ± 13.19	27.20 ± 12.29	24.15 ± 13.19	0.019
Follow-up, month, median (IQR)	23 (14.96–33.15)	25 (18.00–35.00)	22 (14.00–33.00)	

NHA: Nursing home admission; IADL: Instrumental Activities of Daily Living; NPI: Neuropsychiatric inventory; CCI: Charlson comorbidity index; MWI: Multimorbidity-weighted index; HRQOL-CI: Health related quality of life comorbidity index; SD: Standard deviation; IQR: Interquartile ranges

Table 2 The association between comorbidity indices and NHA in AD patients using Cox regression models and competing-risks regression models (*N* = 488)

Comorbidity indices	Cox regression		Competing-risks regression	
	HR (95%)	*p*	SHR (95%)	*p*
CCI as continuous	1.09 (0.97–1.22)	0.13	1.10 (0.98–1.22)	0.09
MWI as continuous	1.05 (1.01–1.08)	0.007	1.04 (1.01–1.08)	0.009
HRQOL-CI as continuous	1.12 (1.04–1.20)	0.002	1.12 (1.04–1.20)	0.002
CCI as categorical:				
0	Reference		Reference	
1	1.19 (0.71–1.99)	0.51	1.19 (0.72–1.98)	0.50
2	0.98 (0.54–1.79)	0.95	0.98 (0.54–1.80)	0.95
≥ 3	1.66 (1.02–2.70)	0.041	1.68 (1.04–2.71)	0.034
MWI as categorical:				
[0–2.23]	Reference		Reference	
]2.23–5.27]	1.58 (0.89–2.80)	0.11	1.55 (0.89–2.71)	0.12
]5.27–9.60]	2.24 (1.27–3.96)	0.005	2.13 (1.21–3.74)	0.009
> 9.60	2.41 (1.36–4.27)	0.003	2.41 (1.36–4.28)	0.003
HRQOL-CI as categorical				
[0–1]	Reference		Reference	
[2–3]	1.27 (0.79–2.03)	0.32	1.23 (0.79–1.92)	0.37
4	1.89 (0.97–3.67)	0.06	1.72 (0.89–3.31)	0.11
≥ 5	2.02 (1.25–3.29)	0.004	1.96 (1.22–3.17)	0.006

CCI: Charlson comorbidity index; MWI: Multimorbidity-weighted index; HRQOL-CI: Health related quality of life comorbidity index; HR: Hazard ratio; SHR: Subdistribution hazard ratio; all models were adjusted for age, sex, education level and the stage of Alzheimer's disease (MCI/dementia)

and HRQOL-CI was associated with NHA compared to lower level of comorbidity burden.

Additional analyses involving NPI as covariate

After adding the NPI score (non-available data for 36 patients) as a covariate, the overall sample size was 452, and 122 (27%) presented NHA. The higher level of comorbidity burden as measured by MWI and HRQOL-CI was associated with NHA compared to lower level of comorbidity burden, while higher level of CCI tended to be associated with NHA compared to the lower level of CCI ($p = 0.07$; additional file 5). After considering mortality as competing event, similar findings were reported (additional file 6).

Discussion

The MWI, the HRQOL-CI and the CCI were not initially designed to predict NHA, nevertheless the present study is going a step further by showing that higher level of these three comorbidity indices was associated with NHA in AD patients. After considering mortality as a competing event, the higher level of the comorbidity

burden as assessed by the three comorbidity indices remained significantly associated with NHA.

Previous studies have reported that comorbidity burden were associated with higher cognitive impairment, higher functional decline and higher neuropsychiatric symptoms in individuals with AD [29]. However, these factors were reported among the common causes of NHA in individuals with dementia [30]. In the present study, the association between comorbidity burden and NHA in AD was significant, after adjustment for the stage of AD and the neuropsychiatric symptoms at baseline. The stage of AD at baseline (i.e. MCI versus dementia) was determined by the memory clinic physician through the cognitive level and the functional decline related to cognitive decline. Therefore, it is possible that higher comorbidity burden may increase cognitive decline leading to functional decline and then NHA. The presence of neuropsychiatric symptoms may not explain our findings because the NPI score at baseline was not associated with NHA. The non-significant effect of the NPI appears not in line with previous studies, and in particular one that was previously carried out on the MEMORA cohort, which reported a significant association between NPI and NHA [30–33]. The difference of the follow-up periods and the characteristics of the patients (i.e. the diagnosis of NCD) could explain the non-significant effect of the NPI in the present study.

In a retrospective study reported by Seibert et al., the association between the CCI as continuous and NHA was significant in a multimorbid dementia population (at least two chronic diseases in addition to dementia) [34]. This association was not examined in the entire sample, but it was examined in six subgroups based on chronic disease combinations (for example dementia with hypertension and diabetes…). While their findings may partially support ours, there are key differences, which may preclude comparaison with our findings. Unlike the study reported by Seibert et al., the present study included AD patients regardless of their chronic conditions. This approach may allow us to better understand whether the comorbidity burden have an impact on NHA in AD patients, without restricting the analyses to patients with at least two chronic conditions.

The three comorbidity indices showed similar performances according to their C-index values. Nevertheless, the higher level of the MWI and HRQOL-CI explained more NHA than the higher level of CCI. This difference in findings across the comorbidity indices may be related to their conceptions: the MWI and the HRQOL-CI were designed to predict functional decline, whereas the CCI was designed to predict mortality. However, functional decline is a common cause of NHA in AD, which may explain why higher level of MWI and HRQOL-CI was more strongly associated with NHA than higher level of CCI. In contrast, the CCI as continuous was not associated with NHA in AD patients as well as the study reported by Mank et al. [33], indicating that the CCI as continuous may not be a good predictor of NHA in AD patients.

Another important point is that a higher comorbidity burden in dementia was frequently associated with an increased risk of mortality [12, 35, 36]. Mortality may therefore represent a competing event influencing the association between comorbidity burden and NHA in our sample. In the present study, the higher level of the comorbidity indices remained significantly associated with NHA in AD patients, even after considering mortality as a competing event. Conversely, in the study reported by Haaksma et al., the association between higher comorbidity burden and institutionalization in dementia was not significant after considering mortality as competing event [12]. Their findings showed a higher institutionalization rate (43% vs. 25.6%) and a higher mortality rate before institutionalization (18% vs. 7.6%) compared to our study. These differences may be partially explained by the heterogeneity of the sample (including various dementia subtypes) and potential outcome misclassification, as their study did not differentiate between nursing homes and sheltered housing.

To the best of our knowledge this is the first study reporting a significant association between higher level of comorbidity burden and NHA in AD patients. However, it remains unclear if the comorbidity burden accelerates cognitive and functional decline related to AD, or if a direct effect of the comorbidity burden on NHA may also exist. Indeed, some comorbidities may affect functional autonomy independently from the NCD [37]. In the present study many factors that could influence the relationship between comorbidity burden and NHA in AD patients were not considered, such as polypharmacy, hospitalization, frailty, or caregiver burden. These non-considered factors may limit our ability to conclude a direct effect of comorbidity burden on NHA in AD patients.

The present study had some limitations that should be considered when interpreting the results. The collection of the comorbidities may not be exhaustive in routine care in the memory center, which may affect the calculation of comorbidity indices and lead to underestimate the comorbidity burden of patients. The diagnosis of AD was not confirmed through the pathophysiological biomarkers (Cerebrospinal fluid or positron emission tomography biomarkers). Only three comorbidity indices were considered in the present study, based on the applicability of indices using databases and the availability of information regarding comorbidities in the MEMORA cohort. However, the use of three comorbidity indices represents a triangulation method that help to confirm our findings

[38]. Moreover, the French Primary Health Insurance Fund database provided data concerning only nursing homes without confusing with other assisted living, reducing bias related to the misclassification of outcome.

Conclusion

In conclusion, our findings highlighted that a higher comorbidity burden, as measured by the CCI, MWI, and HRQOL-CI, was associated with an increased risk of NHA in AD patients. The observed relationship may be partly explained by the cognitive and functional decline linked to comorbidity burden. While the MWI and HRQOL-CI have been less commonly used in previous research, our results support their potential value in assessing comorbidity burden in AD patients and encourage their utilization in future studies. This study have important clinical implications by encouraging physicians to systematically collect comorbidities in patients with AD in memory consultations. However, comorbidity burden is a modifiable risk factor, and implementing targeted interventions to better manage comorbidity burden could help mitigate the risk of NHA in individuals with AD. The use of comorbidity indices, which take multiple health conditions into account, provides a comprehensive view of the patient, making it particularly relevant for both clinical practice and research in memory consultations, as it could enable better monitoring and management of patients with AD.

Abbreviations

AD	Alzheimer's disease
NHA	Nursing home admission
CCI	Charlson comorbidity index
NCD	Neurocognitive disorders
MCI	Mild cognitive impairment
MWI	Multimorbidity-weighted index
HRQOL-CI	Health related quality of life comorbidity index
IQR	Interquatrile ranges
IADL	Lawton instrumental activities of daily living scale
NPI	neuropsychiatric inventory
PAF	Population attributable fraction

Supplementary Information

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Supplementary Material 1

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Author contributions

M.N.T: Conceptualization, Methodology, Data analysis, Writing - Original Draft. A.G.C: Conceptualization, Writing - Review & Editing. C.Mt: Data analysis-Review & Editing. C.Mc: Conceptualization, Methodology, Writing - Original Draft, Supervision. V.D: Conceptualization, Methodology, Data analysis, Writing - Original Draft, Supervision.

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Data availability

The data are not publicly available due to regulations and ethical restrictions.

Declarations

Ethical consideration

Information was individually provided to the patients and caregivers, and oral consent had to be obtained to participate, as required by the French committee for this type of study. The MEMORA cohort protocol (clinicaltrial.gov number NCT02302482) has been approved by the regional ethics committee (Comité de protection des personnes Sud Est III) on July 29, 2014, the Advisory Committee on Information Processing in Material Research in the Field of Health, and the National Commission for Data Protection and Liberties (CNIL). These approvals are in line with the principles of the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest (declared to the corresponding author)

Independent of this work, A.G.C is an unpaid sub-investigator or local principal investigator in NCT04867616 (UCB Pharma), NCT04241068 (Biogen), NCT05310071 (Biogen), NCT03446001 (TauRx Therapeutics), NCT03444870 (Roche), NCT04374253 (Roche), NCT04777396 (Novo Nordisk), NCT04777409 (Novo Nordisk), NCT04770220 (Alzheon), NCT05423522 (Medesis Pharma), NCT06079190 (GlaxoSmithKline).
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Declarations of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the first author (M.N.T) used ChatGPT in order to correct English mistakes. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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