Mediterranean Journal of Clinical Psychology

ISSN 2282-1619

MJCP

Volume 12, n 2, 2024

Clinical Psychology

Relationship between Anxiety, Depressive Symptoms and Mild Neurocognitive Disorder in Older Adults: A Systematic Review

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Abstract

Background: Neurocognitive disorder (NCD) presents its highest prevalence in older adults, with the rate of diagnoses expected to triple in the next two decades due to the accelerated aging of the population. The etiology of this disorder is diverse, with notable comorbidity with anxiety and/or depressive symptoms, and there are modifiable risk factors that highlight significant prevention potential.

Objective: This systematic review aimed to examine the current scientific literature findings to answer the research question: What is the relationship between anxiety and depressive symptoms and mild cognitive impairment?

Methodology: The search was conducted in the Web of Science and Scopus databases in March 2024, using the search equation: ("depressive symptoms" OR "anxiety symptoms") AND ("older person" OR elderly OR aging) AND ("cognitive decline" OR "cognitive performance" OR "mild cognitive impairment"), with a date range from January 2020 to March 2024. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed, and the results were uploaded to the Tree of Science platform.

Results: The resulting articles were organized into three perspectives: Anxiety and depression in mild Neurocognitive disorder, Functional and structural neuroanatomy of mild NCD in relation to anxiety and depressive symptoms, and Predictors and psychosocial profile of mild NCD.

Conclusion: Research confirms a significant relationship between both anxiety and depressive symptoms and mild NCD, though the nature of this relationship is still unclear. Establishing the psychosocial profile of older adults, as a characterization tool, promises to be very helpful for the clinical management of mild NCD and preventing its progression to major neurocognitive disorder (major NCD). The percentage of modifiable risk factors in mild NCD is 40%, presenting a substantial opportunity to reduce the prevalence of neurocognitive disorders in adulthood.

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Keywords:
Anxiety; Clinical Psychology; Depression; Neurocognitive disorder; Psychosocial profile.

Received: 6 June 2024
Accepted: 23 July 2024
Published: 30 August 2024

Citation: Villa Castaño, J. E., Hernández Muñoz, C., & Landínez Martínez, D. (2024). Relationship between Anxiety, Depressive Symptoms and Mild Neurocognitive Disorder in Older Adults: A Systematic Review *Mediterranean Journal of Clinical Psychology 12*(2).
https://doi.org/10.13129/2282-1619/mjcp-4242

1. Introduction

In the late 1980s, the concept of mild cognitive impairment (MCI) was coined by a group from New York University to identify individuals whose cognitive function was not as expected for their age yet did not suffer from manifest dementia (Petersen & Morris, 2005). Recently, the term has been encompassed within neurocognitive disorders (NCD), categorized by severity into mild (mild NCD) and major (major NCD) (APA, 2013). Mild NCD is considered an intermediate stage between expected cognitive aging and major NCD.

The Diagnostic and Statistical Manual of Mental Disorders (APA, 2013) categorizes NCD as disorders where the primary clinical deficit is cognitive function, which is acquired and not developmental, representing a decline from a previously acquired functioning. Mild NCD represents a broad and heterogeneous clinical variety that can be classified into different types: amnestic single domain with memory impairment, amnestic multidomain, non-amnestic single domain, and non-amnestic multidomain. The diagnosis of mild NCD is based on subjective complaints of cognitive decline and must be supported by an objective neuropsychological test confirming it in one or more of six main domains: 1. Complex attention, 2. Executive functions, 3. Learning and memory, 4. Language, 5. Perceptual-motor ability, and 6. Social cognition, with preserved functionality in the instrumental activities of daily living in the evaluated individual (APA, 2013).

Regarding the prevalence of mild NCD, Sachdev et al. (2015) applied uniform criteria to harmonized data from 11 studies in the U.S., Europe, Asia, and Australia, finding a prevalence range from 5% to 36.7%. This high variability may be related to regional and/or ethnic differences, posing problems for public health policies and planning (Sachdev et al., 2015). The Mayo Clinic Study of Aging found that the prevalence of mild NCD is 16% in individuals over 70 years old, clearly a condition related to age. When the evaluation suggests a degenerative etiology, Alzheimer's disease is very likely, with the conversion rate from mild NCD to major NCD varying between 8% and 15% per year, highlighting the importance of early detection to identify NCD subtypes and plan appropriate clinical interventions (Petersen, 2016). The main difference between mild NCD and major NCD lies in the individual's functional performance, with minimal or no functional impairment in mild NCD, while evident functional impairment in major NCD affects the ability to be independent in daily tasks. Mild NCD has become recognized as a pathological condition and not a manifestation of aging, receiving much attention as a clinically useful entity in preventing and formulating therapies to avoid or slow the progression to major NCD (Petersen, 2004).

Significantly, studies report a high comorbidity of depression and mild NCD in older adults, with statistics indicating that for this population, 32% of individuals with mild NCD report depression, while 37% of individuals with depression report mild NCD (Arbeláez et al., 2023; Gómez-Tabares et al., 2024). The order of appearance of these conditions remains largely unknown, meaning it is unclear whether depression precedes or follows mild NCD. Establishing this chronological order is strategic for clarifying the mechanisms of this association and thus for designing clinical interventions (Guo et al., 2023).

Among other possibilities, it is speculated that the depression-mild NCD relationship could be bidirectional (Guo et al., 2023), with two explanatory hypotheses proposed. Firstly, depressive episodes are argued to predispose individuals to cognitive deficiencies that often persist after affective symptoms have disappeared, with chronic alterations in the physiological system and neurochemical components accompanying the onset of depression leading to cognitive decline. Secondly, the cognitive reserve hypothesis suggests that higher intelligence in early life stages is associated with a lower risk of depression in old age, with higher-order cognitive processes and superior neurological integrity explaining this association (Lu et al., 2021).

Regarding anxiety, its relationship with mild NCD is understudied. Nevertheless, the literature has reported that, like depression, anxiety is highly prevalent among people with mild NCD. Specifically, anxiety correlates positively with lower performance in working memory, problem-solving, and processing speed (Butters et al., 2011). Anxiety disorder symptoms are widespread, with prevalence rates in middle-aged and older adults ranging from 15% to 31.1% (Jones et al., 2022). In 70% of the population with mild NCD or major NCD, the literature confirms a prevalence of mild to moderate anxiety symptoms, highlighting the importance of clinical intervention focused on anxiety in the treatment of mild NCD (Pacas Fronza et al., 2024).

The high prevalence of anxiety and depression in older adults with mild NCD suggests that these two conditions somehow affect cognitive function performance. Anxiety may increase the risk of cognitive decline through reduced intellectually stimulating activities, sleep disorders, or benzodiazepine use. Neuropsychiatric studies using a closer measure of anxiety have shown that higher scores are associated with a greater risk of conversion to major NCD. However, there is little literature on the relationship between anxiety and mild NCD, especially in low- and middle-income countries (Smith et al., 2021). On the other hand, clinically relevant depressive symptoms are significantly associated with a decline in cognitive functions, including episodic memory, mental state, and global cognition, independently of other risk factors for cognitive functions (Yang et al., 2020).

Besides anxiety and depressive symptoms, there are other factors associated with the risk of NCD (Nelson et al., 2023; Ranieri et al., 2021). The 2020 Lancet Commission report, based on new reviews and meta-analyses, incorporated an updated model for NCD prevention throughout life with 12 modifiable risk factors representing about 40% of major NCD worldwide, which could be prevented or delayed, indicating high prevention potential, especially in low- and middle-income countries (Livingston et al., 2020). It has become evident that psychosocial factors increase the risk of NCD onset, so profiling individuals with mild NCD considering psychosocial variables makes sense, which could result in a more nuanced understanding of when mild NCD is more likely to progress to major NCD (Siew et al., 2023).

In older adults, the risks of mild NCD onset and conversion to major NCD are higher, and combined with the global aging population, this suggests a significant challenge for health sciences. The psychosocial profiling of individuals with mild NCD in adulthood, as proposed by some authors, is intriguing to better refine intervention plans depending on the profile found, defined by psychosocial variables such as depression, anxiety, quality of life, social support, life satisfaction, and social connectivity (Siew et al., 2023).

As deduced, the etiology of NCD is complex and underpinned by numerous variables. Given the high prevalence rates of mild NCD in older adults and the high comorbidity of this disorder with anxiety and depressive symptoms, the research question arises: What is the relationship between anxiety and depressive symptoms and mild NCD in older adults? Thus, this systematic review aims to investigate and gather scientific findings on this question.

2. Methodology

To examine the relationship between depressive and anxiety symptoms with mild cognitive impairment (mild NCD), the Web of Science (WOS) and Scopus databases were used for reference bibliographic search tools for scientific literature. In both databases, the following search equation was used: ("depressive symptoms" OR "anxiety symptoms") AND ("older person" OR “elderly” OR “aging”) AND ("cognitive decline" OR "cognitive performance" OR "mild cognitive impairment"), with a date range from January 2020 to March 2024.

The WOS database yielded a total of 400 relevant articles, which matched the criteria associated with older adults, depressive and anxiety symptoms, and mild cognitive impairment. These articles were downloaded as a flat file to the Tree of Science platform (Robledo et al., 2014), a tool based on graph theory metrics where articles are nodes and citations between them are links. Each node represents a unit of knowledge visualized as a tree, with roots as classic articles, the trunk as structural articles that enable knowledge branching, and leaves as current

perspectives or trends on the relationship between anxiety and depressive symptoms and mild NCD.

In terms of findings in the Scopus database, the search equation yielded a total of 151 articles, of which 97 were discarded for not being contextually relevant to the relationship between depressive and anxiety symptoms and mild NCD in older adults. Thus, 54 articles were included for subsequent eligibility review (see figure 1).

Combining the two databases used for the search, a total of 551 articles were obtained, of which systematic reviews and articles not matching the thematic criteria were excluded, leaving a final total of 51 articles forming the core of this systematic review (see table 1).

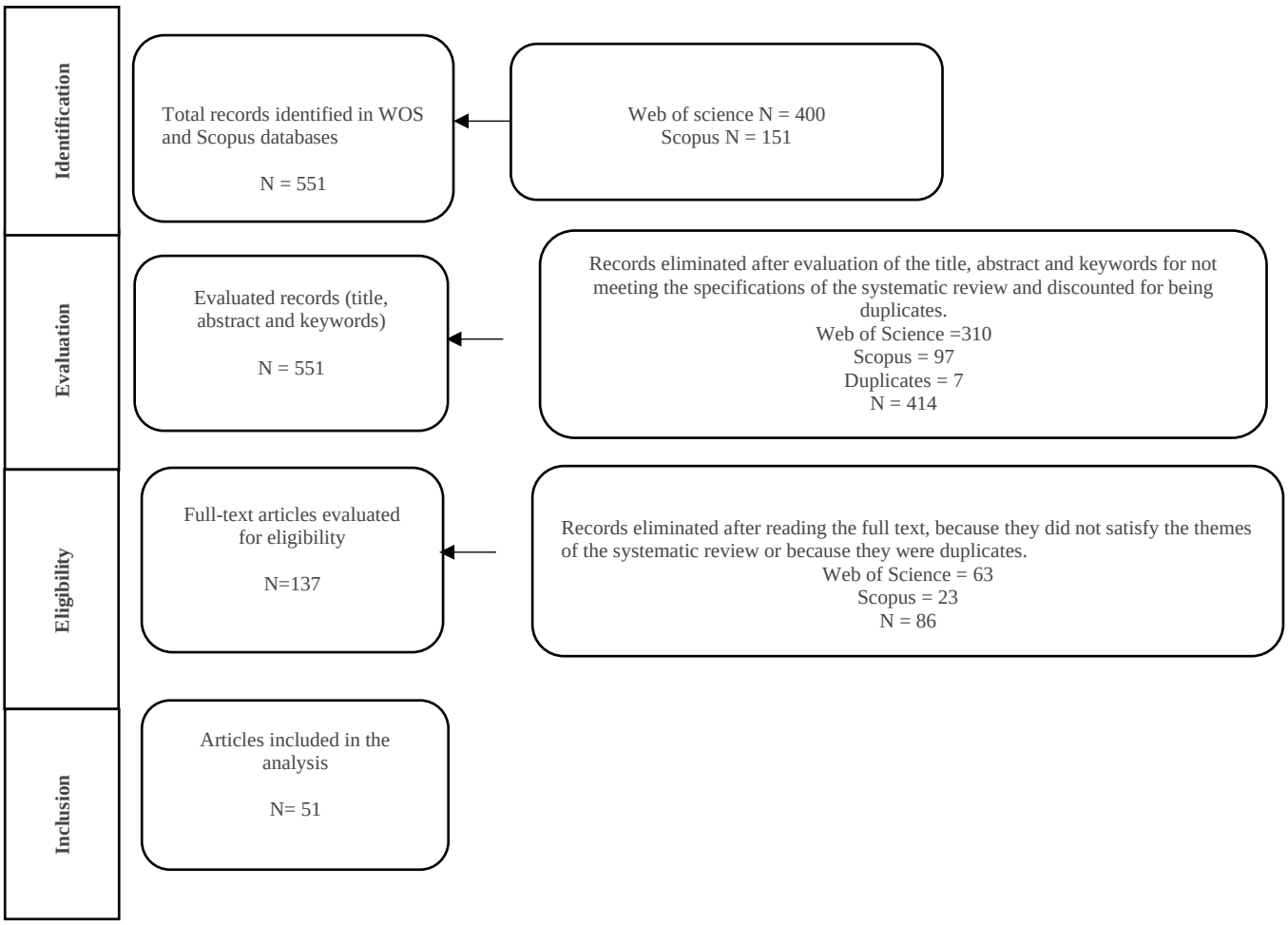

Figure 1. Flow Diagram Illustrating the PRISMA Methodology Followed in the Systematic Review.

Table 1. Articles included in the systematic review

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Article	Country	Population	Age (SD)	Gender Fem N (%)	Conclusion
Aschwanden et al. 2022	USA EUROPE	middle-aged and older adults (23596)	>63	10000(42,4)	The current findings suggest null or unexpected links between personality and memory discrepancy.
Bai et al. 2023	CHINA	CLHLS 9023	80,9(10,1)	4579 (50,7)	Improving sleep quality in older adults may reduce the negative impact of depression and cognition decline
Brenowitz et al. 2021	USA	HABC (2192)	70-79	1161 (53)	Early adulthood depressive symptoms may be a risk factor for cognitive impairment independent of mid- or late-life depressive symptoms.
		CHS (3930)	>65	2259 (57,5)	
Cachón-Alonso et al. 2023	EUROPE	SHARE (55652)	66.3(9.6)	30,418 (54.6)	Loneliness is a psychosocial risk factor for cognitive decline among older adults (≥65 years).
Carmel & Tur-Sinai 2022	ISRAEL	SHARE (11930)	68.9(9.2)	6692 (56,1)	The decline in memory is greater among early retirees than among those who retire on time or later.
Chan et al. 2020	CHINA	To mild NCD (47)	55.2(9.3)	65 (38.5%)	The main finding in the present study was a significant interaction between baseline depressive symptoms and level of AD pathology, as measured by CSF.
		Sustained NC (169)	63.4(9.0)	21 (44.7%)	
Chapman et al. 2022	USA	SCD(136)	73,7(6,8)	92(68)	Individuals who develop AD-associated dementia likely undergo a state of SCD at some point early in the life course.
Chiari-Correia et al. 2023	BRAZIL	NC (19)	70,5(6,9)	13 (68,4)	It is possible to differentiate patients with nDMCI from patients with DMCI using magnetic resonance techniques.
		mild NCD-nD (17)	74.2(6.8)	12 (70,5)	
		mild NCD-D (15)	73.7(6.6)	10 (66,6)	
		AD (14)	75.2(8.6)	10 (71,4)	
Christman et al. 2020	USA	DA (76)	36.2(9.0)	52 (68,42)	BAG showed an interactive effect with depression severity on executive function and working memory performance.
		NDA (94)	30.1(9.2)	58 (61,7)	
		DOA (118)	66.4(5.4)	72 (61)	
		NDOA (36)	70.0 (6.6)	20 (55,6)	
Du et al. 2022	CHINA	HC (70)	75,7(5,3)	31 (44,2)	An important finding of the study worth highlighting is the moderating effect of depressive symptoms on the relationship between FG GMV and MMSE scores
		mild NCD-D (70)	76.8(7,3)	30 (42,8)	
		mild NCD-nD (70)	75.9(6,9)	32 (54,2)	

Freak-Poli et al. 2022	SWEDEN ROTERDAM	RPS (4514)	71(7)	2466 (54,6)	Loneliness, not social support, predicted cognitive decline and the onset of dementia independently of depressive symptoms.
		SNAC (2112)	72(10)	772 (36,5)	
Gao et al. 2022	CHINA	CLHLS(9023)	>65	601 (47,6)	The decline rate of cognitive function in older adults can effectively predict the growth rate of depressive symptoms.
Geraets et al. 2023	ENGLAND	ELSA(7460)	65,7(9,4)	3915 (54,7%)	Modifiable dementia risk factors may be important targets for dementia prevention in people with depressive symptoms during midlife.
Golüke et al. 2022	NETHERLANDS	NCD 1054	81	411 (39)	No association was found between BGC and depressive symptoms.
Greig Custo et al. 2022	USA	CN (HA)(55)	69.9(5.8)		The results demonstrated that the severity of depressive symptoms increased with cognitive deterioration. Higher scores on the total GDS were reported for diagnoses of mild cognitive impairment and dementia compared to CN.
		MCI (HA)(92)	71.2(7.2)		
		Major NCD (HA)(28	71.8(9.7)		
		CN (EA)(41)	70.5(6.4)		
		MCI (EA)(56)	74.6(9.6)		
		Major NCD (EA)(12)	76.3(8.9)		
Guo et al. 2023	USA	DS RS-mild NCD (9317)	64(0,2)	5444 (58,4)	High-risk depressive symptoms are related to a higher risk of subsequent MCI; and MCI predicts subsequent high-risk depression
		mild NCD SDS (9428)	65(0,2)	5374 (57)	
Handing et al. 2023	USA	CG (905)	73,1(2,7)	428 (47,3)	Having less than a high school education and poor self-rated health were significantly related to mild NCD.
		mild NCD (306)	73,6(3,0)	148 (48,3)	
		PD (231)	73,7(2,9)	141 (61,0)	
		PD and CD (110)	74,4(3,0)	67 (60,9)	
Hemphill et al. 2023	USA	PD(487)	61,0 (9,7)	170 (34,9)	Older patients with comorbid depressive symptoms experience greater cognitive decline.
Hill et al. 2021	USA	SCD (28396)	76,0 (?)	16914 (59,5)	Older adults with SCD and depressive symptoms may be at greater risk for poor cognitive outcomes
Hou et al. 2020	CHINA	DS(580)	74,8(3,5)	168 (28,97)	The deterioration of depressive symptoms was associated significantly with faster cognitive decline
Huang et al. 2022	USA	LCP Q1(2858)	72,3(20,7)	1673 (58,54)	Adults with depression may require more medical attention, and early intervention is required to delay the development of cognitive impairment and dementia.
		Q2(2568)	70,2(10,8)	1402 (54,6)	
		Q3(2848)	68,0(10,7)	1633 (57,34)	
		HCP Q4(2113)	64,8(10,1)	1362 (64,46)	
Jing et al. 2023	CHINA	MSCS(2500)	70	1291 (51,64)	The findings highlight the buffering effects of social support utilization on mild NCD in depressed older adults.

Jones et al. 2022	USA	(PBH)63	64,7(8,9)	37 (59)	Elevated depressive symptoms impact cognitive function in non-demented individuals.
Jokisch et al. 2022	GERMANY	No mild NCD (1400)	62,4(7,0)	747 (53)	Depressive symptoms predicted mil NCD in cognitively unimpaired participants of population-based study.
		mild NCDL (147)	65,6(7,6)	76 (52)	
Lang et al. 2021	USA	HA no mild NCD (31)	69,9(6,9)	24 (77,4)	Severity of depressive symptoms was associated with greater cognitive impairment, independent of ethnicity.
		HA mild NCD (73)	72,2(7,4)	43 (58,9)	
		EA no mild NCD (23)	70,3(6,0)	16 (69,6)	
		EA mild NCD (37)	74,9(9,9)	17 (45,9)	
Lee et al. 2021a	USA	A A (93)	68,4(9,6)	63 (71,6)	The importance of considering the unique cultural and historical backgrounds across different racial/ethnic groups when examining cognitive functioning in elderly.
		Chinese Korean (85)	66,5(9,7)	54 (64,3)	
		Vietnamese (65)	67,9(8,5)	34 (52,3)	
Lee et al. 2021b	CHINA	No DS (15455)	75,3(4,9)	9693 (66,8)	Risk of incident dementia varies with presence and resolution of depression at different ages.
		DS (331)	74,3 (5)	252 (73,1)	
		Persistent DS (335)	75,5(4,7)	263 (82,2)	
		Late DS (487)	75,4(5,3)	364 (78,1)	
Li et al. 2024	CHINA	mild NCD-D (175))	69.5(7.8)	54 (30.9)	The elderly with mild NCD combined with depressive symptoms had worse daily spatial skills, worse daily living ability and lower serum ApoB protein levels
		mild NCD-Nd (839)	69.8(8.3)	276 (32.9)	
		for 5 years (321)	NA		
		To Dementia (28)	78.2(7.0)	16 (57,14)	
		mild NCD (293)	69.2(7,4)	206 (70,3)	
Liew 2020	USA	NCD (11781)	70	7825 (66,4)	SCD and anxiety may potentially be useful to identify high-risk populations for preventive interventions and trials
		No NCD (2285)	76	1389 (60,8)	
Moulinet et al. 2022	FRANCE	NC (56)	69.8(5.61)	31 (55,3)	Patients with SCD and ADC had greater depressive symptoms compared to healthy elderly, which was associated with greater amyloid pathology in SCD and with increased episodic memory performance and glucose metabolism in ADC patients.
		SCD (35)	67.5(6.8)	17 (48,5)	
		ADC (56)	71.2(8.7)	25 (44,6)	
Pacas Fronza et al. 2023	AUSTRALIA	(BMC)163	78,1(6,6)	86 (52,8)	Mild to moderate anxiety symptoms were frequent in memory clinic attendees diagnosed with MCI or dementia

Pérez-Blanco et al. 2024	SPAIN	Excluded (98)	NA	NA	In the SCD group, progression to mild NCD was significantly associated with fewer years of schooling, for early prediction, and with increasing age, greater complaints from informants and higher depressive symptomatology for late prediction.
		Stable NC (86)	64,5(8,8)	57 (66,3)	
		NC to SCD (47)	63.5(8.9)	29 (61,7)	
		NC to mild NCD (12)	68.1(9.8)	5(41,7)	
		Stable SCD (81)	66.1(8.3)	62 (76,5)	
		SCD to mild NCD (11)	69.6(8.8)	10 (90,9)	
		SCD to dementia (9)	71.7(3.0)	6 (66,7)	
		mild NCD to major (22)	75.5(5.8)	10 (45,5)	
		SCD to CN (10)	60.3(9.5)	8 (80)	
		to CN or SCD (17)	66.6(7.1)	12 (70,6)	
		mild NCD (42)	71.8(7.3)	28 (69)	
Piers et al. 2021	USA		60,1(9,4)	1055 (53,82)	Elevated depressive symptoms were associated with poorer performance in visual memory, attention, executive function, and visuospatial ability.
		LDS (1670)	61,2(9,3)	849 (50,84)	
		HDS (292)	59,5(9,3)	207 (70,89)	
Rubin-Norowitz et al. 2022	USA	NC (338)	73.7(5,8)	178 (52,7)	The presence of subclinical depressive symptoms was inversely associated with cognition in the memory and FE domains
		a-mild NCD (530)	72.1(7,4)	224 (42,3)	
Siew et al. 2023	SINGAPORE	NC (696)	70,3(5,7)	439 (63,2)	Three different profiles are reported within participants with mild NCD matching a positive, neutral and negative pattern of psychosocial scores
		mild NCD (194)	70,9(7,24)	109 (56,2)	
Schaeffer et al. 2024	USA	NC(325)	78.6(4.9)	197 (60.69)	Personality traits may be useful in improving predictions about who is at greatest risk of developing specific predementia syndromes.
		SCD(53)	78.9(4.7)	36 (68.92)	
Sharifian et al. 2020	USA	WHICA(5458)	76,2(6,7)	3656 (67)	Findings support the view that perhaps depressive symptoms act as a risk factor for cognitive impairment by reducing leisure activity engagement.
Smith et al. 2021	CHINA, GHANA, INDIA, MEXICO, RUSSIA, SOUTHAFRICA	(SAGE)32715	62,(15,6)	16913 (51,7)	Anxiety was associated with a 1.91 times greater likelihood of mild NCD. Behavioral factors and health status had very little influence on this association.
Welstead et al. 2021	UK	HC (215)	76,2(0,7)	115 (53,5)	The highest cases of depressive symptoms baseline scores were associated with a greater likelihood of reversing from mild NCD to healthy cognition.
		mild NCD (20)	76,1(0,7)	7 (35,0)	
		HC to mild NCD (36)	76,3(0,7)	15 (41,7)	
		mild NCD to HC (21)	75,9(0,7)	9 (42,9)	

Wu et al. 2023	CHINA	HC (622)	71.2(6.6)	280 (45.0)	Results suggest that SCD may be a risk factor for objective cognitive impairment and may predict early diagnosis of the AD.
		SCD (478)	73.4(5.9)	253 (52.9)	
Wu et al. 2021	CHINA	LLD(90)	60	69 (76,7)	The relationship between cognition and depressive symptoms is unidirectional. Depressive symptoms may be a risk factor for cognitive decline.
Yang et al. 2020	CHINA	SSD (5037)	57,2(8,9)	2308 (45,82)	These findings suggest a positive association between poorer cognitive function and an increased risk of developing depressive symptoms.
		HDS (2298)	57, 8(8,6)	1352 (58,9)	
Yang et al. 2023	CHINA	(CLHLS)1627	78, 9(7,7)	904 (55, 56)	Relevant depressive symptoms were associated with poorer cognitive functions and moderately faster cognitive decline
Zaheed et al. 2023	USA	(HRS)2595	64(6.7)	1673 (64.5)	This study adds to the growing literature on insomnia as a contributing factor to cognitive decline among older adults.
Zahodne et al. 2021	USA	Black (241)	74,4(6,3)	165 (68,8)	Having a stronger network of friends is prospectively associated with less episodic memory impairment, above and beyond other positive psychosocial factors-
		Hispanic (159)	75,8(6,2)	103 (65,4)	
		White (178)	73,8(5,8)	98 (55,1)	
Zhang et al. 2020	CHINA	SSD AB+(357)	72,7(7,1)	153 (42,8)	The interaction between Aβ, time, and SSD were significant for global cognition and episodic memory indicates that Aβ-positive status and SSD have a specifically negative effect on cognitive performance
		SSD AB-(234)	71.7(7.6)	114 (48,71)	
		HC AB+(154)	75.3(6.2)	77 (50)	
		HC AB-(138)	72.2(6.1)	62 (44,9)	
		No AB results (305)	NA	NA	
Zhang et al. 2022	CHINA	LDS (3206)	57,3(8,6)	1275 (39,8)	Interventions targeting to alleviating cognitive decline should be given priority among individuals with deterioration of depressive symptoms
		MDS (3747)	58(8,2)	1879 (50,1)	
		IDSC (899)	58 (8,2)	572 (63,7)	
		DDS (929)	58,4 (8,6)	536 (57,7)	
		HDS (483)	58,6(8,1)	337 (69,8)	
Zhou et al. 2021	CHINA	CLHLS(4771)	62,7(5,7)	1897 (39,76)	This study preliminary prompted severe depressive symptoms associated with worse cognitive performance.
Zhu et al. 2022	KOREA	KLSA(8021)	60,3(10,1)	4.369 (54,5)	A higher life satisfaction score was associated with a 19% lower risk of suffering from dementia
Zhu et al. 2023	USA CHINA ENGLAND	HRS USA (8284)	60,1(9,2)	5354 (64,6)	This study suggests that long-term cumulative depressive symptoms were associated with subsequent faster cognitive decline and greater risks for dementia.
		ELSA (4314)	60,1(8,8)	2483 (57,6)	

Zuidersma et al. 2022	NETHERLAND	8	61-83	4 (50)	Nature and direction of the temporal associations between depressive symptoms, cognitive performance and sleep differed between individuals.

Abbreviations: NC = normal cognition; mild NCD-nD = non-depressive mild neurocognitive disorder; mild NCD-D = depressive mild neurocognitive disorder; AD = Alzheimer's disease; CLHLS = chinese longitudinal healthy longevity study; SHARE = survey of health, ageing and retirement in Europ; ELSA England longitudinal study of ageing; PD = parkinson disease; MSCS = multistage cluster sampling; PBH = patients Buttler Hospital; BMC = Brisbane memory clinic; WHICA Washington heights inwood Columbia aging project; SAGE = study on global ageing and adult health; NA = not applicable; DA = depressive adults; NDA = non-depressive adults; DOA = depressive older adults; NDOA = non-depressive older adults; LDS = low depressive symptoms; HDS = high depressive symptoms; SSD AB+ = sub-syndromal depressive symptoms with amyloid positive; SSDAB- = sub-syndromal depressive symptoms with amyloid negative; HC AB+ = healthy cognition amyloid positive; HC AB- = healthy cognition amyloid negative; AB = amyloid; HC = healthy cognition; HA = Hispanic American; EA = European American; mild NCD = mild neurocognitive disorder; SCD = subjective cognitive decline; ADC = Alzheimer's disease continuum; a- mild NCD = amnestic mild neurocognitive disorder; CG = control group; PD = physical deterioration; CD = cognitive deterioration; PRS = Rotterdam Population Study; SNAC = The Swedish National Study on Aging and Care; LCP = low cognitive performance; HCP = high cognitive performance; Q = quartile; LPS = low depressive symptoms; MDS = medium depressive symptoms; IDS = increasing depressive symptoms; DDS = decreasing depressive symptoms; HDS = high depressive symptoms; DS RS-mild NCD = depressive symptoms at risk of subsequent mild neurocognitive disorder; mild NCD SDS = mild neurocognitive disorder subsequent depressive symptoms; HRS USA = Health and Retirement Study USA; ELSA = English Longitudinal Study of Aging; DS = depressive symptoms; WDS = without depressive symptoms; HABC = Health, Aging, and Body Composition; CHS = Cardiovascular Health Study; fMRI = functional magnetic resonance imaging; GDS = geriatric depression scale; CDR = clinical dementia rating; MMSE = mini mental state examination; CT = computed tomography; BGC = basal ganglia calcification; BAG = brain age estimation; MOCA = Montreal cognitive assessment; CIRS = cumulative illness rating scale; EM = episodic memory; EF = executive function; SP = processing speed; WM = working memory; MRI = magnetic resonance imaging; NT = neuropsychological test; CESD = center for epidemiological studies depression scale; APOE = genotype; NPI-Q = neuropsychiatric inventory questionnaire; CSF-AB = cerebrospinal fluid amyloid beta; PET = positron emission tomography; ADAS-13 = Alzheimer's disease assessment scale-cognitive subscale; HVLT-R = Hopkins verbal learning test-revised; TMT = trail making test; HAM-D = Hamilton depression scale; WMH = white matter hyperintensities; MADRS = Montgomery-Åsberg depression rating scale; ADL = activities of daily living; BDT = block design test; VF-CS = verbal fluency category switch; BAI = Beck anxiety inventory; AV = amygdala volume; MHT-11 = mental health test at 11; HADS = hospital anxiety and depression scale; SPPB = short

physical performance battery; DSST = digit symbol substitution test; IPIP = international personality item pool; MMI = multimorbidity index; QSCD = questionnaire on subjective cognitive decline; AS = age stereotype; EAB = essential aging beliefs; SA = subjective age; IGEI = identification with age group; CF = cognitive function; MD = memory decline; IADL = instrumental activities of daily living; EURO D = depression measure; RALVT = Rey auditory verbal learning test; WAIS III = subtests of digit span and visual-spatial ability; CTT = divided attention; WHICAP = episodic memory, language, and visual-spatial functioning; NIH EMOTION = neuropsychological tools for social relationships assessment (i.e., emotional support, friendship, and instrumental support); LS = life satisfaction; HACP = harmonized cognitive assessment protocol; JSQ = Jenkins sleep questionnaire; BECSI = brief cognitive screening inventory; QCSS-E = rapid cognitive screening scale for older adults; CNT = central neuropsychological test; PSQ = sleep quality index; HAMD = Hamilton anxiety scale; LIBRA = lifestyle for brain health; PSA = presence of anxiety symptoms; PHQ-9 = patient health questionnaire; EMQ-R = everyday memory questionnaire; LLD = Late life depressive; HRS = health and retirement study; KLSA = Korean longitudinal study of ageing.

3. Results

3.1 Anxiety and depression in mild NCD in older adults

A total of 25 articles were included in this trend, reflecting a total evaluated population of 205,318 older adults with an average age of 68.92 years and a female component of 53.8%. Twenty-one articles are dedicated to the relationship between depression and mild NCD, and only four articles refer to anxiety and its relationship with mild NCD. This indicates that anxiety has been a poorly studied factor regarding mild NCD in older adults, despite literature reporting a high prevalence of anxiety among neuropsychiatric symptoms in mild NCD, with some studies reporting anxiety-related symptoms in 75% of patients with mild NCD (Rozzini et al., 2008).

Regarding the association of mild NCD with anxiety, a first analyzed study involving 63 people over the age of 50 investigated the relationship between subclinical anxiety and verbal fluency. The sample was characterized by individuals reporting "minimal" to "moderate" anxiety symptoms but who were neither diagnosed nor treated for any anxiety disorder. Despite the initial hypothesis of the researchers, the study did not prove that higher levels of subclinical anxiety symptoms were a significant risk factor for cognitive functioning, including verbal fluency (Jones et al., 2022).

In another hand, a study that included 14,066 participants over 50 years old, residing in the United States, and diagnosed with normal cognition at the beginning of the study, followed for 14 years, established the relationship between the presence of anxiety and the perception of subjective cognitive decline (SCD) with a higher likelihood of developing mild NCD and major

NCD compared to individuals who did not report the presence of SCD or anxiety during the measurement period. The researchers included SCD as part of the report from individuals seeking health services to prevent neurocognitive disorders and highlighted the importance of including the study of anxiety symptoms as an additional risk factor for the evolution from SCD to mild or major NCD (Liew, 2020).

Furthermore, Smith et al. (2021) analyzed cross-sectional, community-based, nationally representative data from the WHO Study, with 32,715 people of various nationalities over 60 years old and residents of several countries, showing that older adults from low and middle-income countries with anxiety symptoms are twice as likely to suffer from mild NCD. Several mechanisms could explain the positive association between anxiety and mild NCD. First, the presence of anxiety is associated with a reduced functional state in performing daily activities in older adults. Moreover, the reduction in daily activities may be associated with an increased risk of mild NCD due to reduced brain stimulation. Secondly, studies have reported that the use of anxiolytics, such as benzodiazepines, is associated with an elevated risk of mild NCD (Smith et al., 2021).

A study based on data from 163 people, with an average age of 78 years, attending a memory clinic with a prior diagnosis of mild or major NCD, found that over 70% experienced mild to moderate anxiety, concluding the importance of including support for managing anxiety symptoms in individuals diagnosed with mild or major NCD due to the presence of such symptoms as a subclinical factor of the main condition (Pacas Fronza et al., 2024).

Regarding depression and its relationship with mild NCD, 21 articles have established significant relationships between the presence of depressive symptoms and mild NCD in older adults. The association between depressive symptoms and the development of major NCD has led to ongoing debate about the direction of causality in this association. Depression could be a risk factor for the onset of major NCD, an early sign or a prodromal stage of major NCD, or it could occur in a state of cognitive decline as a reaction to cognitive or functional disabilities (Jokisch et al., 2022).

A study conducted on 4,771 older adults over 60 years old in China found that subjects with depressive symptoms of depression had poor cognitive function, with the latter being much worse in those meeting the diagnostic criteria for depression. This indicates that more severe depressive symptoms in older adults were associated with poorer cognitive function. This study established that 4.46% of older adults have depression, and 35.19% have depressive symptoms,

with this group showing impairments in orientation, memory, attention, and language tests (Zhou et al., 2021).

Similarly, a study with a Chinese adult population, including 7,335 participants, demonstrated a positive association between clinically relevant depressive symptoms and cognitive functions, including episodic memory, mental state, and global cognition, regardless of other risk factors for cognitive functions. The presence of depressive symptoms was associated with a slightly faster decline in episodic memory, mental state, and global cognition (Yang et al., 2020).

Another study conducted in a Chinese community with 580 older adults over 70 years old divided participants into two groups. The first group consisted of individuals with stable depressive states, and the second group had increasing depressive symptoms over three years. These groups were assessed using a dementia scale to measure cognitive functions and the Chinese Geriatric Depression Scale to identify the presence or absence of depressive symptoms. Researchers found that individuals in the group with depressive symptoms at the beginning of the study tended to have better cognitive function initially but experienced progressively greater cognitive decline proportional to the increase in depressive symptom severity, compared to the stable depression group. However, they noted that more analysis is needed to explore the relationship between depression as a risk factor for the onset and progression of mild NCD with a longer follow-up period (Hou et al., 2020).

Additionally, a prospective cohort study involving 10,387 older adults over 45 years old for 10 years demonstrated that participants with poorer cognitive function had a higher risk of depressive symptoms. Moreover, a positive association was observed between the initial level of depression and the decline in cognitive function during the follow-up period. Researchers indicated that the early onset of depressive symptoms was associated with a greater decline in cognitive performance during the follow-up period, and a higher level of depression accelerated the cognitive decline process (Huang et al., 2022).

Similarly, a study conducted in China with middle-aged and older adults detected differential associations between depressive symptom trajectories and various cognitive aspects. On one hand, a significantly greater degree of executive function decline was found in the subpopulation with increasing depressive symptoms compared to those without associated depressive symptoms. Researchers observed a lower rate of executive function decline among individuals with decreasing depressive symptoms, concluding that depression was an early manifestation of cognitive decline rather than its cause. Additionally, participants with high or moderate depressive symptoms also showed a relatively small increase in cognitive decline rate, indicating

another possible mechanism, where depressive symptoms could be a risk factor for subsequent cognitive decline. Researchers clarified that findings providing insights into the association mechanism between depression and cognition may depend on different cognitive dimensions and highlighted the need for more biological studies to confirm this hypothesis (Zhang et al., 2022).

Accordingly, a study conducted in the United States with 9,317 adults over 20 years, based on a longitudinal survey, found a significant bidirectional association between depressive symptoms and mild NCD. This study examined the association using a competing risks model, establishing the evolution of cognitive performance in response to initial depressive symptoms and the evolution of affective state in response to cognitive complaints at the beginning of the measurement period. The findings supported the bidirectional link between variables, with high-risk depressive symptoms related to a higher risk of subsequent mild NCD, and mild NCD predicting subsequent high-risk depression (Guo et al., 2023).

One of the investigations by Barnes et al. (2012) identified two different trajectories associated with depression or depressive symptoms. The first identified symptoms present previously in participants when they were between 40 and 50 years old, and the second included symptoms perceived in older age. Thus, 13,535 people were included in the study. Data were collected from previous databases with medical checkups and tests conducted between 1964 and 1973, when participants were between 40 and 50 years old. Later, in older age and over a 6-year follow-up period, researchers concluded that people with a higher risk of developing major NCD were those with depressive symptoms during adulthood and old age (80%), followed by those with depressive symptoms in old age (70%), compared to the group that only showed depressive symptoms during adulthood (20%).

This suggests that the presence of depression in older age or sustained depression over long periods increases the risk of developing mild NCD up to major NCD. These results are consistent with the study by Lee et al. (2021a), who also concluded that late-onset depression is a prodrome of major NCD.

Recently, studies like Yang et al. (2023) suggest a positive association between poorer cognitive function and a higher risk of depressive symptoms. Moreover, researchers included important covariates to consider for future programs and research, such as marital status, economic situation, physical and recreational activity, which influence cognitive status. In the same line, a study identified the interrelations between cognitive performance and depressive symptoms in older adults from the general population. Interventions targeting specific cognitive symptoms

(language and attention) have the potential to alleviate depressive and cognitive symptoms in this population. Additionally, improving sleep quality in older adults may reduce the negative impact of depression and cognitive decline on quality of life (Bai et al., 2023).

3.2 Functional and structural neuroanatomy of mild neurocognitive disorder (mild NCD) in relation to anxiety and depressive symptoms

Eleven articles investigate the functional and structural neuroanatomy of mild NCD in relation to depressive symptoms, including 7,549 older adults with an average age of 68.7 years, 57.9% of whom are female. The scope of the studies is to find associations between depression, cognitive function, and how these are reflected through alterations in brain structures, using magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques, as well as through the detection of biomarkers in cerebrospinal fluid (CSF).

For anxiety and its association with mild NCD, only one article was found, which, in a sample of 63 individuals with an average age of 64.76 years and 59% female, proposes to examine the relationship between anxiety symptoms, verbal fluency (VF), and amygdala subregion volumes (Chiari-Correia et al., 2023).

Chiari-Correia et al. (2023) explore the functional and structural differences in the brains of non-depressed mild NCD patients (nD-mild NCD) and depressed mild NCD patients (D-mild NCD), examining the relationship of both groups with Alzheimer's disease (AD) atrophy patterns and cognitive functioning. Compared to the nD-mild NCD group, D-mild NCD patients had more pronounced atrophy in the hippocampus and amygdala, as well as asymmetric damage in the limbic-frontal white matter connection. Cortical thickness was lower for the nD-mild NCD and AD groups compared to the normal cognition (NC) reference group. MRI techniques can differentiate nD-mild NCD from D-mild NCD patients, contributing to better characterization of mild NCD subtypes.

Accordingly, a study evaluating the cross-sectional and longitudinal association of sub-syndromic depression symptoms (SSD) with cognition and brain structures, and exploring whether amyloid (AB) load modifies these associations, indicates that SSD at the start of observation contributed to the development of AD and mild NCD, as well as brain atrophy, both independently and in the presence of AB. Interaction between SSD and initial AB load affected cognition in older adults without dementia. Higher initial scores on the Geriatric Depression Scale (GDS) were associated with decreased cognition, especially in the presence of abnormal AB load. Depressive symptoms were linked to cognitive impairment and atrophy in

the hippocampus and middle temporal gyrus, suggesting that treating depressive symptoms might help delay or slow cognitive decline (Zhang et al., 2020).

Du et al. (2022) report that, for the D-mild NCD group, there was a significant decrease in gray matter volume (GMV) in the bilateral parahippocampal gyrus (PHIP), bilateral fusiform gyrus (FG), and bilateral inferior temporal gyrus (ITG) compared to the nD-mild NCD and NC groups. They note that the positive association between FG GMV and cognitive function is moderated by depressive symptoms in old age, indicating that this relationship varies and may have clinical implications for interventions in patients with severe depressive symptoms and mild cognitive impairment in advanced stages of life.

Chan et al. (2020), examine the combined effects of depression and AD pathology, measured by amyloid AB and Tau biomarkers in cerebrospinal fluid (CSF), on the risk of progression from normal cognition (NC) to the onset of mild NCD symptoms, also attempting to examine the relationship between initial depressive symptoms and the rate of change of biomarkers in CSF. Of 216 individuals in the study sample, 169 (78.3%) remained cognitively normal and 47 (21.7%) later developed symptoms of mild or major NCD, with older age, higher CSF Tau levels, and lower CSF AB levels than normal.

The authors report that depressive symptoms and AD neuropathology were associated with mild NCD, however, they found no evidence of interaction of depressive symptoms and neuropathology associated with dementia, stressing that the main finding was the significant interaction between baseline depressive symptoms and level of AD pathology, measured by CSF, indicating that higher initial HAM-D (Hamilton Depression Scale) scores were significantly associated with an increased risk of clinical symptom onset among individuals with "low AD pathology", but not in "high AD pathology". One possible explanation is that, among individuals with higher levels of AD pathology, the effects of depression on the risk of progression to mild cognitive impairment are overshadowed by the well-established risks associated with the presence of a high burden of AD pathology. However, in individuals with low AD pathology, depressive symptoms may serve as an additional risk factor for the onset of cognitive symptoms (Chan et al., 2020).

A study with 147 subjects, divided into three groups as follows: 56 control group with normal cognition (NC), 35 in the subjective cognitive impairment (SCD) group and 56 in the Alzheimer's disease continuum (ADC) group, aims to evaluate the links between depressive and anxiety symptoms and cognition, along with brain integrity measures across the clinical continuum from NC to AD dementia, to improve understanding of the relevance of

psychoaffective mechanisms in the preclinical and clinical stages of AD. Analyses showed that SCD and ADC patients presented more depressive symptoms than CN patients, with higher depressive symptoms associated with higher AB amyloid load in the SCD group. On the contrary, in the ADC group such symptoms were associated with better episodic memory performance and higher glucose metabolism and tended to be related to better global cognition. In the SCD group, higher SDs were associated with greater AB amyloid deposition mainly in the temporo parietal insular cortex, medial temporal and right hippocampus, while in the ADC group, depressive symptoms were related to higher glucose metabolism in the following brain regions: bilateral precuneus, the retrosplenial posterior cingulate area, the left temporal, superior parietal and temporal regions and the left hippocampus (Moulinet et al., 2022).

Regarding the findings, the authors refer that the positive relationship between episodic memory performance and depressive symptoms in patients in the ADC group was not expected, so they hypothesize a possible anosognosia, suggesting that ADC patients with better cognitive and/or memory performance are more aware of their cognitive difficulties and show more depressive symptoms, or conversely, that those with greater cognitive/memory deficits are more anosognosic and report fewer depressive symptoms. As for anxiety symptoms, a trend toward a positive association with global cognition was found within the SCD group (Moulinet et al., 2022).

Rubin-Norowitz et al. (2022) indicate that subclinical depressive symptoms are inversely associated with memory and executive function domains, a significant association in both AD and non-AD pathology groups. As well, Christman et al. (2020) suggest that a greater discrepancy between estimated brain biological age and chronological age predicts conversion from mild cognitive impairment to dementia, highlighting the role of structural MRI in analyzing markers of accelerated aging providing new insights into the interactions between aging, depression, cognition and disability.

Finally, there is a study investigating the possible underlying neurobiological basis of the relationship between subclinical anxiety and the verbal fluency test with category change (VF-CS), highlighting the authors that a better understanding of the link between subclinical anxiety and cognitive function could be useful for the older adult who needs to minimize the possible effects of anxious symptomatology on cognitive impairment. Contrary to the stated hypothesis, higher levels of subclinical anxiety were not a significant risk factor for cognitive functioning, including FV. Results also revealed that minimal to moderate levels of untreated and undiagnosed anxiety symptoms did not correspond with total amygdala volume or a lower VF-

CS score in the sample studied (Jones et al., 2022). The findings indicate that larger medial central amygdala (CMA) volume, rather than basolateral amygdala (BLA) volume, showed a significant relationship with higher VF-CS scores. Although left and right CMA volumes predicted VF-CS, right hemisphere CMA volume uniquely predicted VF-CS after the effects of left hemisphere CMA volume were controlled for (Jones et al., 2022).

3.3 Predictors and psychosocial profile of mild NCD

Fourteen studies focus on identifying predictors and the psychosocial profile of mild NCD in older adults, with a total evaluated sample of 100.167 individuals from America, Europe, and Asia, averaging 70.29 years old and 54.7% female. Ten articles focus on predictive variables and general risk factors for mild NCD, while the remaining four address its psychosocial profile.

Findings on predictors of mild NCD indicate that age, cardiovascular diseases, and depressive symptoms are significant in the transition from NC to mild NCD. A longitudinal study of 292 individuals born in Lothian (UK) found that 74% remained cognitively healthy, 12% transitioned to mild NCD, 7% reverted to healthy cognition, and 7% maintained mild NCD. Logistic regression evaluated the effect of several predictors on cognitive status progression, reversion, or maintenance (Welstead et al., 2021).

Geraets et al. (2023) calculated individual exposure to modifiable risk factors for major NCD using the Lifestyle for Brain Health Index (LIBRA) (Deckers et al., 2015), including diabetes, chronic kidney disease, coronary artery disease, cognitive and social activity, depression, healthy diet, hypertension, obesity, smoking, hypercholesterolemia, physical inactivity, and alcohol consumption. Higher LIBRA scores correlated positively with cognitive decline. Their aim was to establish to what extent the increased risk of major NCD in depression is explained by modifiable risk factors, the results indicated that during 61,311 person-years, 306 individuals (4.1%) developed dementia, depressive symptoms correlated with higher LIBRA scores, in total 10.4% of the risk of dementias was mediated by differences in LIBRA score and 89.6% was attributed to a direct effect of SDs (Geraets et al., 2023).

Subjective cognitive complaints, premorbid personality traits, life satisfaction, and insomnia symptoms are reported as preclinical indicators of mild NCD. A study on subjective cognitive decline (SCD) explored its neurocognitive characteristics and correlation with mild NCD, negative emotions, and sleep quality, aiming to enhance primary care physicians' awareness and evaluation capacity of SCD. SCD incidence was significantly related to objective cognitive function, negative emotions, and sleep disorders (Wu et al., 2023). Another study simultaneously evaluated risk factors associated with mild NCD and physical decline, finding that older age,

lower education level, and poor self-rated health were the most significant risk factors (Handing et al., 2023).

Regarding the psychosocial profiles of mild NCD, a door-to-door survey in Singapore with 902 individuals (average age 70.48 years) found a 21.5% prevalence of mild NCD, correlating with lower education and less social support. Three distinct psychosocial profiles emerged within the mild NCD group: positive (45.2%), neutral (38.5%), and negative (16.3%), with no significant differences in demographic or cognitive variables (Siew et al., 2023). This classification could benefit future research on mild to major NCD progression, suggesting that a range of factors predicts cognitive decline rather than any single variable having a large impact. Psychosocial profiles were determined by assessing depression using the Geriatric Depression Scale; anxiety using the Geriatric Anxiety Inventory (GAI); quality of life (QOL) using the QOL assessment for older adults, perceived social support, life satisfaction, and social connectivity, along with demographic variables.

Zahodne et al., (2021) report that, in a diverse sample of 578 individuals, having a stronger network of friends is prospectively associated with less episodic memory decline, beyond other factors like positive psychosocial aspects, depressive symptoms, chronic illnesses, and baseline episodic memory. General social support moderates the relationship between depressive symptoms and cognitive function, reducing the likelihood of mild NCD in older adults aged 60-69 and over 80, though objective support increases the risk in depressed individuals aged 70-79 (Jing et al., 2023).

Loneliness is another predictor of mild NCD development. A study found that loneliness is prospectively associated with major NCD, though neither social nor structural support was associated with mild NCD (Freak-Poli et al., 2022). Other authors conclude that loneliness predicts low cognitive functioning in older adults, clarifying that loneliness is a psychosocial risk factor for mild NCD development, emphasizing the importance of social contact formation and maintenance for cognitive health (Cahcón-Alonso et al., 2023).

4. Discussion

This systematic review evaluated the existing literature to establish the relationship between anxious and depressive symptoms and mild neurocognitive disorder (mild NCD) in older adults. A total of 51 studies met the evaluation criteria. The research focuses on clarifying the mechanisms triggering the continuum from mild to major NCD, aiming for early diagnosis to design and implement timely clinical interventions, reverse mild NCD to healthy cognition, or

stop or slow its progression to major NCD. The reviewed studies highlight three main perspectives:

- Anxiety and depression in mild NCD.
- Functional and structural neuroanatomy of mild NCD in relation to anxious and depressive symptoms.
- Predictors and psychosocial profile of mild NCD.

Findings indicate that although anxious symptoms are present in older adults with mild NCD, there is limited research examining the relationship between the two conditions. Studies suggest that older adults with anxiety are more likely to suffer from mild NCD in middle- and low-income countries, highlighting the need for future research to clarify whether preventing or addressing anxious symptoms in the mild NCD population can prevent its progression.

Literature reports a significant relationship between the volume of the centromedial amygdala (CMA) and verbal fluency with category change, implying that CMA volume is specifically a neuromarker of anxiety symptoms. This positive relationship between CMA volume and cognitive performance may be mediated by acute autonomic activation (Jones et al., 2022). It is noted that patients in memory clinics diagnosed with mild or major NCD present subclinical anxiety symptoms, which has important clinical implications for interventions (Pacas Fronza et al., 2024).

Scientific literature is more abundant on depressive symptoms and its relationship with mild NCD, identifying two research trends: one examining the nature of the association and the other studying its neural correlates. First, studies show contradictory results regarding the association between depressive symptoms and mild NCD, with the coexistence of both conditions seeming to increase the risk of major NCD. Statistics indicate that the prevalence of depression among older adults with mild NCD is 32%, while 37% of those with depression are diagnosed with mild NCD. It remains unclear whether depression precedes mild NCD or appears afterward. Resolving this question will impact intervention approaches, although it is considered more important to address the comorbidity of depression and mild NCD to positively affect patient outcomes (Guo et al., 2023).

The association between depressive symptoms and mild NCD might be bidirectional since cognitive and emotional functions in the brain operate together within the frontoparietal limbic system. This system involves cognitive function controlling posterior pathways to maintain and regulate relevant information, while emotions influence cognition through the limbic system

(prefrontal and perceptive cortex). Three possibilities in the literature for the relationship between depressive symptoms and mild NCD are: 1) depression predicts memory deficits, but memory deficits do not predict depression, 2) mild NCD predicts depression, but depression does not predict mild NCD, 3) neither depression nor mild NCD predicts each other (Guo et al., 2023).

Regarding functional and structural neuroanatomy of mild NCD in relation to anxious and depressive symptoms, studies using multimodal magnetic resonance imaging (MRI) techniques have demonstrated improved ability to characterize brain structures and analyze brain functionality in patients with mild NCD with and without depressive symptoms. Specifically, Chiari-Correi et al., (2023) found that the depressive mild NCD group had lower hippocampal and amygdala volumes compared to the control group, showing lower intensities than major NCD patients. The main differences between the mild NCD groups without depression and with depression were found in the posterior medial areas of the brain, with significant differences in the lingual gyrus and the isthmus of the cingulate gyrus, in addition the average values of cortical thickness and volume in these areas were very close to the control group in mild NCD with depression, highlighting that the lingual gyrus had a positive correlation with the values of the geriatric depression scale. The combination of increased hippocampal atrophy and preservation of the lingual gyrus appears to be key to depressive symptoms in older individuals with major NCD (Chiari-Correia et al., 2023).

In line with the above, in the study by Du et al. (2022), a decrease in gray matter volume (GMV) in the fusiform gyrus (FG) was reported in depressive and non-depressive mild NCD patients compared to the control group. The FG, one of the first regions affected by cognitive decline, correlated with global cognition measured by the MMSE. Moreover, functional magnetic resonance imaging evidence supports the role of the FG in the processing of emotional information. The authors speculate that FG atrophy may be closely related to emotion recognition and cognitive function.

Another research states that improving the knowledge of cognitive and brain substrates across the clinical continuum from normal cognition to major NCD is relevant for clinical management. Depressive symptoms were associated with a higher amyloid burden in patients with subjective cognitive decline (SCD) and better episodic memory and metabolism in patients with Alzheimer's disease continuum (ADC). These findings suggest that depressive symptoms reflect different processes throughout the course of Alzheimer's disease (AD), where higher symptoms reflect a greater likelihood of a biomarker of AD in the SCD stage, while conversely

they would reflect a greater awareness of cognitive deficits associated with a less severe cognitive stage of the disease in ADC patients, indicating the importance of evaluating and managing depressive symptoms in SCD and mild NCD to improve prevention and prognosis (Moulinet et al., 2022).

Concerning the predictors and psychosocial profile of mild NCD, some studies investigate potential factors involved in the onset, reversal, stabilization, and progression of mild NCD to major NCD. Others suggest characterizing individuals with mild NCD through psychosocial profiles for better clinical intervention planning.

A study on a highly phenotyped cohort reported a slow but steady increase in mild NCD rates over six years, with 4% of participants improving from mild NCD to healthy cognition (CS). Particularly, higher initial depressive symptoms were associated with a greater likelihood of reverting to CS, suggesting the potential of early detection and treatment of depression to prevent mild NCD. Age, cardiovascular history, and the number of depressive symptoms differed among transition groups of mild NCD. Older age was linked to lower chances of maintaining mild NCD or returning to CS, and cardiovascular history increased the likelihood of maintaining mild NCD (Welstead et al., 2021).

Several studies review sociodemographic conditions and lifestyle factors to determine risk factors associated with mild NCD. Modifiable risk factors are important targets for preventing cognitive decline in older adults (Geraets et al., 2023). Modifiable risk factors represent 40% of major NCD worldwide, suggesting high prevention potential, especially in low- and middle-income countries where prevalence is higher. The 12 modifiable risk factors identified are low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution (Livingston et al., 2020).

Specifically, psychosocial profiling aims to develop intervention models tailored to the psychosocial profiles of mild NCD patients. Since most mild NCD subjects are unlikely to progress to major NCD, intervention efforts should focus on those with negative psychosocial profiles to achieve the best results in halting cognitive decline (Siew et al., 2023). The researchers divided the mild NCD group into three well-differentiated psychosocial profiles: positive (45.2%), negative (16.3%), and neutral (38.5%). Anxiety, depression, quality of life, perceived social support, life satisfaction, and perceived social connectivity formed the psychosocial assessment, suggesting different implications of mild NCD on well-being. The neutral and positive profiles, not associated with significant dysfunctions, indicate that most individuals with

mild NCD may have minimal daily functioning and quality of life impact. Negative profiles, associated with depressive symptoms and reduced quality of life, present the highest risk of progressing to major NCD. Psychosocial profiles can capture the different reactions people have to their mild cognitive impairment, although it may be that different psychosocial functioning occurs independently of cognitive impairments (Siew et al., 2023).

Overall, the research confirms a significant relationship between anxious and depressive symptoms and mild NCD, though the nature of this relationship is still unclear. Correlational studies, neuroimaging evidence, and prevalence and comorbidity data suggest that interventions targeting anxious and depressive symptoms can be crucial for developing prevention, promotion, and early diagnosis programs for mild NCD. Additionally, establishing the psychosocial profile of older adults as a characterization tool promises to be very helpful in managing mild NCD and preventing its progression to major NCD. Considering that 40% of mild NCD risk factors are modifiable, the potential for reducing the prevalence of neurocognitive disorders in adulthood represents a significant opportunity.

5. Strengths and limitations

Strengths: the good availability of scientific literature found in the databases for the last five years is highlighted, with some of the studies being pioneers in the inclusion of new covariates that are suspected of influencing the appearance of the neurocognitive disorder; The research comes from both high-, middle- and low-income countries, and it is notable that the prevalence of neurocognitive disorder is higher in the latter two; It is important to highlight the importance of functional magnetic resonance studies that allow establishing the neuronal correlates associated with the neurocognitive disorder. In consideration of the limitations: the multicausality of the neurocognitive disorder and therefore the large number of associated covariates make it a complex entity in its study and understanding, in addition to the great ethnic and cultural variety that represent an additional challenge now. to harmonize the measurement batteries and their cut-off points to conceptualize a possible diagnosis of neurocognitive disorder. The nature of the neurocognitive disorder mainly requires the development of longitudinal research, which is why research must be carried out with follow-up of several years.

6. Conclusion

Anxious and depressive symptoms present a significant comorbidity with neurocognitive disorder; however, research does not end up clarifying the relational nature between these pathologies. In any case, the neurocognitive disorder is heterogeneous in nature and can affect

one or more cognitive domains, with its etiology being multicausal. The approach of psychosocial characterization of adults and the elderly with or without neurocognitive disorder is suggested as a very helpful tool for the design of promotion, prevention and intervention programs of the continuum that goes from healthy cognition to neurocognitive disorder, especially considering the factors of modifiable risks, since early detection of cognitive decline is strategic to reduce the high prevalence rates of neurocognitive disorder.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

Author contributions

JEV: Data collection, analysis and interpretation of results, all authors reviewed the results and approved the final version of the manuscript. CHM: Data collection, analysis and interpretation of results, all authors reviewed the results and approved the final version of the manuscript. DLM: Draft manuscript preparation, data collection, analysis and interpretation of results, all authors reviewed the results and approved the final version of the manuscript.

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DOI: 10.13129/2282-1619/mjcp-4242