

The Neurobiological Pathway Towards Suicidal Ideation

- Cerebrospinal Fluid Markers, Cognitive Impairment and Brain Imaging

Irma Rymo

Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg



UNIVERSITY OF GOTHENBURG

Gothenburg 2025

© Irma Rymo 2025
irma.rymo@gu.se

ISBN 978-91-8115-274-6 (PRINT)
ISBN 978-91-8115-275-3 (PDF)

Printed in Borås, Sweden 2025
Printed by Stema Specialtryck AB



"Happiness can be found, even in the darkest of times, if one only remembers to turn on the light"

J.K. Rowling

Alexander, my precious son, may your path in life always be guided by resilience, filled with prosperity, and lit by boundless joy

The Neurobiological Pathway Towards Suicidal Ideation

- Cerebrospinal Fluid Markers, Cognitive Impairment and Brain Imaging

Irma Rymo

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and
Physiology
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

In recent years, there has been increasing recognition of neurobiological factors as critical contributors to the vulnerability underlying suicidal behavior. This thesis examines the associations between synaptic dysfunction, mild cognitive impairment, structural brain changes, and suicidal ideation within population-based samples of older adults.

Paper I included 86 women from the year 1992 cohort of the Prospective Population Study of Women (PPSW), all of whom participated in psychiatric assessments and underwent lumbar puncture (LP). *Paper II* involved 916 participants drawn from both the PPSW and the year 2000 cohort of the Gothenburg H70 Birth cohort study. Cognitive status was evaluated using the Winblad et al. criteria. *Paper III* investigated 322 participants from the 2014 cohort of the Gothenburg H70 Birth Cohort Study who also underwent LP. *Paper IV* included 774 individuals from the same cohort who underwent brain magnetic resonance imaging (MRI).

Paper I identified elevated cerebrospinal fluid (CSF) levels of YKL-40 and GAP-43 in women reporting past month suicidal ideation. Higher CSF GAP-43 levels were also related to feelings of worthlessness. *Paper II* found that mild cognitive impairment (MCI) was associated with life-weariness and death wishes reported within the past year, as demonstrated in adjusted regression models. MCI was also related to lifetime experiences of life-weariness. *Paper III* identified a connection between high CSF Ng level and lifetime reports of life-weariness, death wishes, and thoughts of taking one's own life, that remained after taking CSF levels of A β 42, T-Tau, and P-Tau into account. *Paper IV* found that individuals with a lifetime history of serious suicidal ideation exhibited larger white matter lesions (WML) volumes compared to those without such ideation. However, this association did not persist after adjusting for relevant covariates in the logistic regression model.

To conclude, these findings suggest that neurobiological factors—including synaptic dysfunction, cognitive impairment, and distinct structural brain changes—may contribute to suicidal ideation among older adults.

Keywords: suicidal ideation, synaptic dysfunction, mild cognitive impairment

ISBN 978-91-8115-274-6 (PRINT)

ISBN 978-91-8115-275-3 (PDF)

SAMMANFATTNING PÅ SVENSKA

På senare tid har allt mer fokus riktats mot möjliga biologiska faktorer bakom självmordsbeteenden. Den här avhandlingen undersöker sambandet mellan hur förändringar i nervcellernas struktur och funktion, förekomst av kognitiva nedsättningar samt strukturella förändringar i hjärnan påverkar förekomsten av självmordsbeteenden. Avhandlingen är baserad på medborgare bosatta i Göteborg och syftar till att återspegla den allmänna befolkningen på ett representativt sätt.

Studie I fann förhöjda nivåer av markörerna YKL-40 och GAP-43 i ryggmärgsvätskan bland kvinnor med självmordstankar och känslor av värdelöshet under den senaste månaden, vilket signalerar förekomst av inflammation i hjärnan samt en nedsatt signalöverföring i de områden där hjärnans nervceller kommunicerar med varandra.

Studie II visade att deltagare i tidigt skede av demenssjukdom oftare rapporterade förekomst av livsleda och dödsönskan jämfört med deltagare utan kognitiva nedsättningar. Självrapporterade kognitiva nedsättningar var i högre grad relaterade till självmordstankar jämfört med nedsättningar som fastställts objektivt genom skattningar. Försämrat minne och förmåga att uppfatta form, storlek och rymd mellan föremål var också i större utsträckning relaterat till självmordstankar än andra typer av kognitiva nedsättningar.

Studie III visade förhöjda nivåer av neurogranin i ryggmärgsvätskan hos deltagare som bejakat livsleda, dödsönskan eller självmordstankar. Fyndet pekar återigen på en försämrad signalöverföring mellan hjärnans nervceller hos individer med självmordstankar. Inget samband påvisades mellan markörer som avspeglar neurodegeneration (den process där nervceller gradvis bryts ned och dör, vilket är typiskt vid demenssjukdomar), och förekomst av självmordstankar.

Studie IV påvisade en ökad förekomst av vitsubstansförändringar bland deltagare som någon gång under livet allvarligt övervägt att ta sitt liv jämfört med de deltagare som inte haft någon sådan livshistorik. Sambandet kvarstod emellertid inte efter att hänsyn tagits till potentiellt bidragande faktorer.

Sammanfattningsvis antyder fynden att förändringar i nervcellernas funktion, förekomsten av kognitiva nedsättningar samt strukturella förändringar i hjärnan kan bidra till självmordstankar bland äldre personer.

LIST OF PAPERS

- I. Rymo, I., Kern, S., Bjerke, M., Zetterberg, H., Marlow, T., Blennow, K, Gudmundsson, P., Skoog, I., Waern, M. CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. *Acta Psychiatrica Scandinavica* 2017; 135(4): 121–133.
- II. Rymo, I., Fässberg, MM., Kern, S., Zetterberg, H., Skoog, I., Waern, M., Sacuiu, S. Mild cognitive impairment is associated with passive suicidal ideation in older adults: A population-based study. *Acta Psychiatrica Scandinavica* 2023; 148(1): 91–101.
- III. Rymo, I., Zetterberg, H., Blennow, K., Kern, S., Skoog, I., Sacuiu, S, Waern, M. High CSF neurogranin level is related to lifetime reports of passive suicidal ideation in a population-based sample of older adults. *Journal of Psychiatric Research* 2025; 181: 340–347.
- IV. Rymo, I., Zetterberg, H., Westman, E., Skoog, I., Waern, M., Sacuiu, S. Brain morphology and suicidal ideation; a population-based MRI study. Submitted.

CONTENTS

Sammanfattning på svenska	viii
List of papers	ix
Contents	x
Abbreviations	xii
Definitions in short	xiv
Introduction	15
Risk factors for suicidal behavior	15
Terminology and assessment of suicidal behavior	17
Neurobiological explanation models	18
Neuroinflammation and suicidal behavior	19
Neuroanatomical correlates of suicidal behavior	20
Isolated cognitive impairments and suicidal behavior	21
Mild cognitive impairment and suicidal behavior	22
Alzheimer’s disease and suicidal behavior	23
Neurobiological models examined in this thesis	23
Markers of neuroinflammation and suicidal behavior	24
Markers of synaptic dysfunction and suicidal behavior	25
Markers of myelin damage and suicidal behavior	25
Markers of neurodegeneration and suicidal behavior	26
MCI and suicidal behavior	26
Markers of Alzheimer’s disease and suicidal behavior	27
Brain Morphology visualized by MRI and suicidal behavior	27
Aim	30
Participants and Methods	31
Ethical considerations	31
Participants	32
Procedures	33
Instruments	33

Diagnosis.....	36
Assessment of suicidal thoughts and behaviors	36
CSF Analysis.....	37
MCI diagnosis and impairments in specific cognitive domains	38
MRI examinations	39
Statistics.....	40
Results	42
Paper I.....	42
Paper II	43
Paper III.....	45
Paper IV.....	47
Discussion	48
Paper I.....	48
Paper II	49
Paper III.....	51
Paper IV.....	52
Strengths.....	54
Limitations.....	55
Conclusion.....	56
Future perspectives.....	58
Acknowledgement.....	59
References	60

ABBREVIATIONS

AD	Alzheimer's disease
ATC	Anatomical therapeutic chemical classification code
BMI	Body mass index
CSF	Cerebrospinal fluid
CNS	Central nervous system
CPRS	Comprehensive psychopathological rating scale
GAP-43	Growth-associated protein-43
LP	Lumbar puncture
MADRS	Montgomery-Åsberg depression rating scale
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
NfL	Neurofilament light chain
Ng	Neurogranin
PPSW	Prospective Population Study of Women
YKL-40	Chitinase-3-like protein 1

DEFINITIONS IN SHORT

Major depression

A mood disorder characterized by depressive symptoms changes in sleep patterns, appetite fluctuations, difficulties with concentration, fatigue, feelings of worthlessness or excessive guilt, psychomotor agitation or retardation, and recurrent thoughts of death or suicide. A diagnosis required at least five of these symptoms to be present during the same two-week period, with at least one being either depressed mood or loss of interest. In this thesis, major depression was diagnosed according to the DSM-IV criteria.

Minor depression

A mood disorder requiring the presence of two to four depressive symptoms during the same two-week period, representing a change from previous functioning. At least one of the symptoms must be either depressed mood or loss of interest or pleasure. In this thesis, minor depression was diagnosed according to the DSM-IV research criteria.

INTRODUCTION

Suicidal behavior represents a critical global public health issue, responsible for over 700,000 deaths annually. Despite a promising global decline of approximately 36% in suicide rates between 2000 and 2019, suicide remains one of the leading causes of death worldwide. Suicide rates are highest among older adults and tend to increase with advancing age (1). Sweden mirrors this global pattern, having seen a peak in suicide rates during the 1970s followed by a sustained decline. Nonetheless, suicide continues to represent a significant cause of mortality in the country, with approximately 1 200 deaths registered annually (2).

Each suicide constitutes a significant public health tragedy, exerting profound and enduring impacts on families, communities, and society at large. This underscores the urgent need to deepen our understanding of the mechanisms underlying suicidal behavior. Despite extensive research, critical knowledge gaps remain, particularly concerning the neurobiological underpinnings of suicidal behavior. Addressing these gaps is essential not only for advancing scientific insight but also for informing the development of effective treatments and public health strategies aimed at reducing suicide risk.

RISK FACTORS FOR SUICIDAL BEHAVIOR

Given the extensive and growing body of research on risk factors related to suicidal behavior, this section provides a focused summary of such factors that have been previously identified in the literature and for which we had relevant data available. The selection of potential confounders was guided by the specific objectives of each analysis.

Worldwide, individuals aged 70 and older consistently exhibit the highest rates of suicide (1), underscoring the importance of age as a key variable in the study of suicidal behavior. Older adults are generally less likely than younger individuals to disclose suicidal thoughts, yet they remain disproportionately affected (3). They are also more likely to employ highly lethal methods and demonstrate a stronger intent to die following a suicide attempt (4-6). In Sweden, the suicide mortality rate among men aged 75 and above was reported to be 28 per 100 000 while those aged 85 and above show the highest rates

nationwide, with 43 deaths per 100 000. These figures contrast remarkably compared to the national age-standardized suicide rate of 15 per 100 000 for both sexes (2).

Gender differences in suicidal behavior are evident across patterns of ideation, attempts, and mortality. Women are more likely to report experiencing suicidal thoughts, whereas men have a higher likelihood of dying by suicide—a discrepancy commonly referred to as the *gender paradox in suicide* (7). Although suicide attempts are more frequently reported among women, men typically exhibit suicide completion rates that are two to three times higher, a disparity often linked to the use of more immediately lethal means (8).

Over the past few decades, a substantial body of research has identified marital status as an important factor associated with suicide risk. Individuals who are unmarried, divorced, or widowed—especially older men who have lost a spouse—appear to be at elevated risk of suicide (9). In contrast, being married or living with a partner is generally associated with a lower risk and is considered a protective factor (10).

Substance use—particularly alcohol consumption—has been strongly linked to suicidal behavior. This association is largely attributed to alcohol's capacity to lower inhibitions, impair judgment, and serve as a maladaptive strategy for coping with psychological distress (11). Supporting this, a Swedish autopsy study found that alcohol was detected in nearly 40% of individuals who died by suicide (12).

Findings from observational literature indicates that low educational attainment may serve as a significant risk factor for suicidal behavior across the lifespan (13, 14), potentially contributing to the disparity in mortality across socioeconomic strata (15). However, the relationship between education level and suicidal behavior is intricate and possibly confounded by cognitive performance, which is strongly associated with both educational attainment (16) as well as suicidal behavior (17).

Major depressive disorder (MDD) is widely regarded as the psychiatric condition most strongly linked to suicide, with estimates indicating its presence in over 80% of suicide deaths (18). In addition to completed suicides, recent meta-analyses have reported that approximately 53.1% of individuals with MDD experience suicidal ideation, and 31% have attempted suicide (19, 20).

However, it is important to note that a substantial proportion of individuals with suicidal thoughts do not fulfill the diagnostic criteria for MDD (21).

TERMINOLOGY AND ASSESSMENT OF SUICIDAL BEHAVIOR

The terminology surrounding suicidal behavior has long been debated and remains a subject of ongoing scholarly discussion, with terms such as “suicidality” and “suicidal behavior” often used interchangeably over time. Currently, there is still no universally accepted approach for assessing or defining suicidal behavior, posing a challenge as well as limitation when comparing research outcomes across studies. In response, The Columbia Classification Algorithm of Suicide Assessment (C-CASA) (22) has sought to establish a consistent terminology for describing suicidal behavior. According to this framework, suicidal behavior includes:

- 1) Passive suicidal ideation: Involves thoughts of death or a desire to be dead without specific plans
- 2) Active suicidal ideation: Refers to thoughts involving a desire to die with a specific plan or intent
- 3) Suicide attempt: An act of self-harm with a clear intention to die
- 4) Completed suicide: A fatal outcome resulting from a suicide attempt

A widely used tool for assessing suicidal behavior, particularly in routine clinical practice, is the suicidality item from the Montgomery-Åsberg Depression Rating Scale (MADRS) (23). This item specifically evaluates the presence of suicidal thoughts as one of the subcomponents in the assessment of current depressive symptoms. Respondents rate the severity of suicidal thoughts on a scale from 0 to 6 as follows:

0-1: Enjoys life or takes it as it comes

2-3: Weary of life. Only fleeting suicidal thoughts

4-5: Much better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intentions

6: Explicit plans for suicide when there is an opportunity

The term “suicidal feelings” also appears frequently, particularly in research settings, and was originally introduced and conceptualized by Paykel in 1974 through the development of the Paykel questions (24). This instrument consists of five hierarchical yes/no questions designed to assess suicidal thoughts and behaviors across different timeframes (past week, past month, past year, or lifetime). Respondents are asked whether they have:

1. Felt that life was not worth living
2. Wished they were dead
3. Had thoughts of taking their own life
4. Seriously considered taking their own life
5. Made a suicide attempt

NEUROBIOLOGICAL EXPLANATION MODELS

Emerging evidence suggests that neurobiological processes—particularly those involving immune activation, cognitive dysfunction, and structural brain changes—contribute to the diathesis of suicidal behavior (25). This section begins by examining neuroinflammation as a potential central mechanism and then considers its downstream effects, including impaired synaptic function, cognitive decline, and morphological brain alterations. These interconnected pathways form the theoretical foundation for the four studies included in this thesis, each examining these mechanisms in relation to suicidal behavior through analyses of CSF biomarkers, cognitive assessments, and neuroimaging.

NEUROINFLAMMATION AND SUICIDAL BEHAVIOR

Neuroinflammation is defined as the activation of immune processes within the central nervous system (CNS), which encompasses the brain and spinal cord. It represents the CNS's innate response to various conditions, including trauma, infections, environmental factors (Figure 1) (26). When acute and properly regulated, these inflammatory responses play a vital role in preserving neural integrity and promoting repair processes (27). Glial cells—including microglia, astrocytes, and oligodendrocytes—are pivotal players in neuroinflammation, each contributing uniquely to the brain's immune response and maintaining neural health (28).

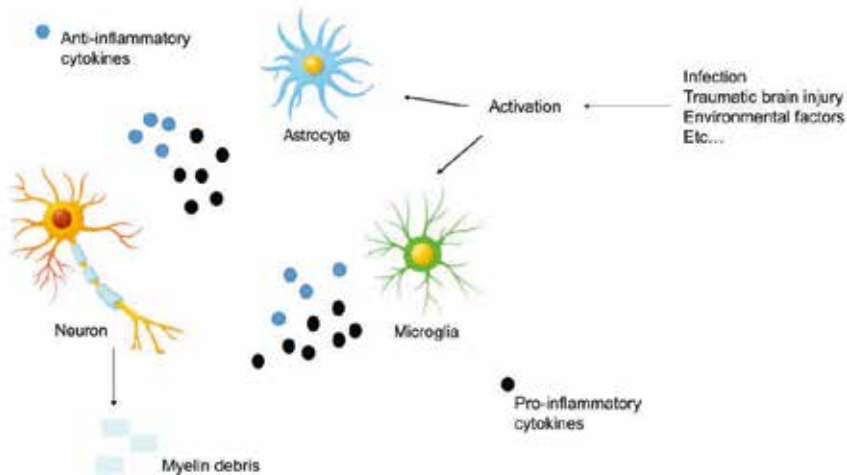


Figure 1. Illustration of the neuroinflammatory process. Original by the author.

During neuroinflammation, microglia serve as the first line of defense, releasing signaling molecules such as cytokines. They also clear damaged synapses, promote the formation of new neural circuits, and support overall brain plasticity (29).

Microglia also contribute to the maturation of astrocytes and modulate their role in the immune system (30). Astrocytes release cytokines, maintain the chemical environment required for neuronal function, and support synaptic connections. They are vital for preserving neural communication and facilitating neuronal plasticity and function (31).

Similarly, microglia are essential for facilitating the maturation of oligodendrocyte in their myelination of axons (32). During inflammatory responses, both microglia and astrocytes become sources of pro-inflammatory cytokines, such as TNF- α , IL-2 and IL-6 (29, 33, 34). These molecules can disrupt synaptic function, impair neuroplasticity, and promote neuronal degeneration—processes closely linked to cognitive decline and mood disorders—and may ultimately contribute to structural changes in the brain over time (26, 35-37).

In recent years, a growing body of research has consistently associated inflammation with suicidal behavior (38-40). Early clinical studies involving patients treated with interferon-alpha (IFN- α) therapy indicated that proinflammatory cytokines may contribute to the emergence of suicidal ideation (41, 42). Subsequent studies have supported these findings, reporting elevated levels of soluble IL-2 receptors in the blood and increased concentrations of IL-6 in the CSF of individuals who have recently attempted suicide. (43, 44). Moreover, individuals who have attempted suicide have been shown to exhibit higher plasma concentrations IL-6 and TNF- α , compared to both non-suicidal depressed patients and healthy controls (45).

NEUROANATOMICAL CORRELATES OF SUICIDAL BEHAVIOR

Post-mortem studies of individuals who died by suicide have suggested that microglial activation may contribute to behavioral changes underlying suicidal behavior (46, 47). Notably, evidence of microgliosis has been observed in the orbitofrontal cortex (OFC) (48), dorsolateral prefrontal cortex (DLPFC) (49), anterior cingulate cortex (ACC) (49, 50), and mediodorsal thalamus (49) in individuals who died by suicide (Figure 2). These areas have in common that they facilitate adaptive, flexible behaviour in the face of changing contingencies and guide decision-making (51-56)]—abilities that are referred to as cognitive functions (57). Dysfunction in these abilities might mediate

suicidal behavior as a consequence of an impaired capacity to respond in a functional manner when faced with challenging environmental stimuli.

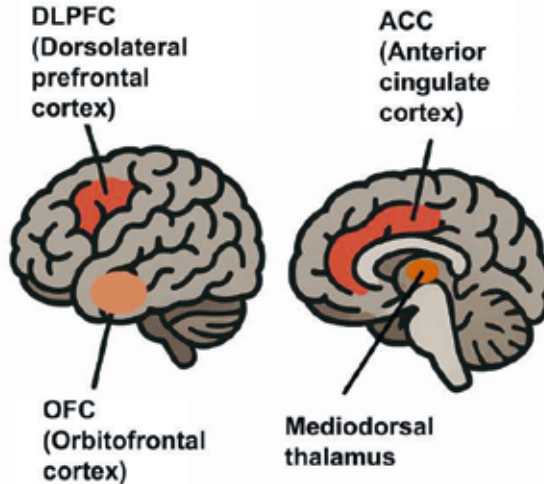


Figure 2. Illustration of the brain regions previously associated with neuroinflammation among individuals who have died by suicide. Original by the author.

ISOLATED COGNITIVE IMPAIRMENTS AND SUICIDAL BEHAVIOR

Several studies have examined how suicidal behavior may relate to impairments in executive function. Findings indicate that individuals with depression who have attempted suicide, both in older adult cohorts (60+) and across mixed age groups, demonstrate poorer decision-making abilities compared to control subjects (58-60). Cognitive inhibition has also been found to be impaired in suicide attempters aged 65 and above, compared to both non-depressed individuals and depressed individuals without a history of suicidal behavior (61). Moreover, older adults with depression and a history of suicide attempts have consistently demonstrated poorer performance on tasks requiring executive control when compared to their non-attempting peers (17, 62). Authors of previous clinical studies have proposed that deficits in the

different subdomains of cognitive competence may compromise an individual's ability to cope with stress effectively, thereby increasing susceptibility to suicidal behavior.

However, interpreting these findings is complicated by the confounding effects of depression, which is strongly associated with both suicidal behavior and cognitive dysfunction—especially within executive function domains (63, 64).

A limited number of non-clinical and population-based studies have sought to examine the association between cognitive impairment and suicidal behavior, aiming to disentangle this relationship from the overlapping effects of depression. One prospective study in older adults found that poorer executive functioning at baseline was linked to a markedly increased risk of suicide over a mean follow-up period of 4.9 years, although neither suicidal ideation nor behavior were predictive of suicide in that sample (65). In a separate population-based study of individuals aged 50 and over, deficits in time orientation were uniquely associated with passive suicidal ideation, while other domains showed no relationship (66). In contrast, another study involving participants aged 50–64 and 65 years and older found no associations between global cognitive functioning—including short-term memory, working memory, and verbal fluency—and either passive or active suicidal ideation (67).

MILD COGNITIVE IMPAIRMENT AND SUICIDAL BEHAVIOR

Beyond impairments in specific cognitive domains, exploring the association between suicidal behavior and mild cognitive impairment (MCI) may provide critical insight into how early-stage cognitive decline influences suicidal behavior. MCI is generally regarded as an intermediate stage between normal aging and dementia, characterized by measurable cognitive deficits that do not significantly interfere with daily functioning (68). Importantly, individuals with MCI often retain insight into their cognitive decline while remaining functionally independent—a combination that may heighten psychological distress, perceived loss of autonomy, and ultimately, vulnerability to suicidal ideation and behavior.

ALZHEIMER'S DISEASE AND SUICIDAL BEHAVIOR

Building on the role of neuroinflammatory processes in suicidal behavior and the relevance of early-stage cognitive decline, Alzheimer's disease (AD)—the most common form of dementia—represents a critical condition in which these pathways converge (69). As a progressive neurodegenerative disorder, AD is characterized by both synaptic dysfunction and sustained microglial activation (70), processes that are also implicated in the neurobiology of suicide (46). The pathological accumulation of amyloid-beta 42 (A β 42), due to disrupted production and impaired clearance, leads to plaque formation and triggers chronic neuroinflammation, particularly in early stages of the disease (71). AD is also frequently accompanied by neuropsychiatric symptoms such as depression and impaired decision-making (72), both of which are established risk factors for suicidal behavior (73).

Understanding the relationship between dementia and suicidal behavior has been challenging and where previous research has yielded conflicting findings so far (74, 75). The variability in findings may stem from differences in study populations, the absence of universally accepted diagnostic standards for both dementia and suicidal behavior, and insufficient consideration to the different stages of cognitive decline. However, a recent meta-analysis indicates that while suicidal thoughts and attempts appear to be less frequent among individuals with advanced dementia, they may occur more often during the initial phases of cognitive impairment (76).

NEUROBIOLOGICAL MODELS EXAMINED IN THIS THESIS

The subsequent sections present an overview of the specific neurobiological systems and biomarkers that have been investigated in connection with suicidal ideation, as explored within the scope of this thesis.

MARKERS OF NEUROINFLAMMATION AND SUICIDAL BEHAVIOR

YKL-40, or chitinase-3-like protein 1 (CHI3L1), is a glycoprotein that has been recognized as a biomarker of neuroinflammation and impaired synaptic function (Figure 3) (77).

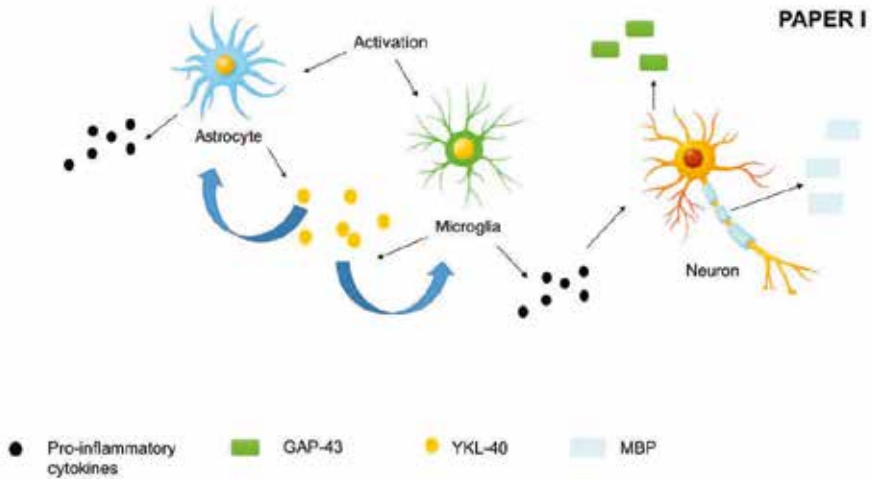


Figure 3. Illustration of neuroinflammatory processes involving activated glial cells and associated biomarkers. Original by the author.

Increased concentrations of YKL-40 have been detected near amyloid plaques and neurofibrillary tangles in individuals with AD, and elevated levels have also been reported in the CSF of individuals with MCI (78). Higher CSF levels of YKL-40 have also been suggested as a potential marker for differentiating individuals with AD from cognitively healthy individuals, and for forecasting the progression of cognitive decline in those with MCI into AD (78). Furthermore, increased CSF YKL-40 levels have been associated with several other, both acute as well as chronic, neuroinflammatory conditions in the CNS (79). The relationship between CSF levels of YKL-40 and suicidal behavior has not been explored in prior research.

MARKERS OF SYNAPTIC DYSFUNCTION AND SUICIDAL BEHAVIOR

Growth Associated Protein 43 (GAP-43) is a presynaptic protein critical for axonal growth and synaptic plasticity (Figure 3) (80). It plays a key role in maintaining synaptic function and is highly expressed in brain regions central to cognitive processing, such as the hippocampus, neocortex, and cerebellum (81-83). GAP-43 levels have been examined in post-mortem studies of individuals with depression who died by suicide, although findings have been mixed (84, 85). To date, GAP-43 has not been studied in connection with suicidal behavior in non-clinical populations.

Neurogranin (Ng) is a postsynaptic protein (Figure 4) that interacts with calmodulin and is predominantly found in excitatory neurons within the neocortex, amygdala, and hippocampus (86). It plays a key role in synaptic plasticity and memory consolidation by modulating calmodulin activity, which is crucial for long-term potentiation (LTP) (87). Despite its significance in these neural processes, its potential involvement in suicidal behavior remains unexamined.

MARKERS OF MYELIN DAMAGE AND SUICIDAL BEHAVIOR

Myelin Basic Protein (MBP), predominantly produced by oligodendrocytes in the CNS, is crucial for the formation and maintenance of myelin sheaths (Figure 3). These sheaths insulate axons, support structural stability, and facilitate the rapid conduction of nerve impulses (88). Postmortem studies have reported decreased levels of MBP in individuals with depression who died by suicide (84). Additionally, MBP has been linked to neuroinflammatory processes associated with neuronal damage (89) and has more recently been proposed as a potential biomarker for predicting suicide risk in clinical populations (90).

MARKERS OF NEURODEGENERATION AND SUICIDAL BEHAVIOR

Neurofilament light chain (NfL) (Figure 4) is a component of the neuronal cytoskeleton of large-calibre myelinated axons and facilitates conduction velocity and maintained morphological integrity (91). The release of NfL from neurons and into the CSF upon axonal damage is seen in a wide range of neurodegenerative diseases, making CSF NfL a general marker of neuro-axonal damage (92, 93).

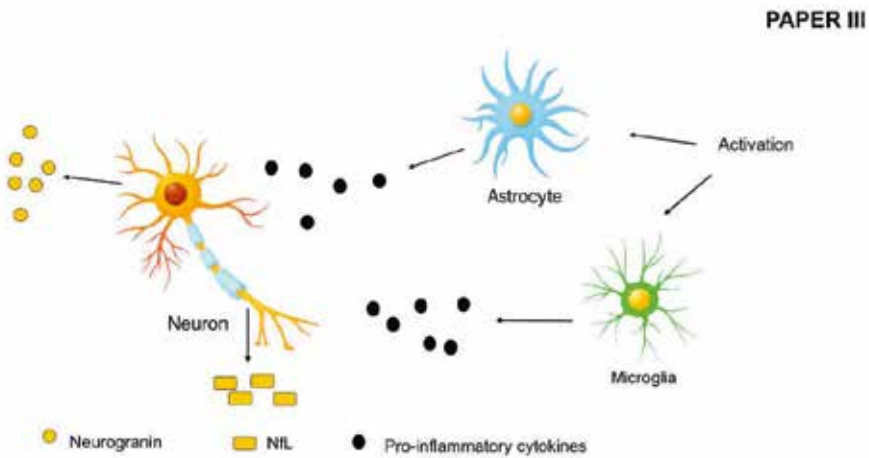


Figure 4. illustration of glial activation and associated neuronal biomarkers. Original by the author.

Elevated serum levels of NfL have previously been observed among depressed suicide attempters, compared to healthy subjects (94). However, NfL has not yet been examined in relation to suicidal behavior in non-clinical populations.

MCI AND SUICIDAL BEHAVIOR

Research in this area has been limited by inconsistent definitions of MCI across studies, leading to challenges in comparing findings. To address the lack of

uniformity in diagnosis, the international consensus criteria proposed by Winblad and colleagues introduced a standardized framework (95). These criteria require the person to 1) be neither cognitively intact nor demented, 2) cognitive deterioration either shown by objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits and 3) activities of daily living to be preserved and complex instrumental functions to be either intact or minimally impaired.

To date, the relationship between MCI—when defined according to these standardized criteria—and suicidal behavior has not been systematically examined.

MARKERS OF ALZHEIMER'S DISEASE AND SUICIDAL BEHAVIOR

Total tau (T-tau) is widely recognized as a general indicator of neuronal damage when elevated in CSF or blood. Phosphorylated tau (P-tau), on the other hand, is regarded as a more specific biomarker for AD. A typical AD biomarker profile includes reduced CSF levels of A β 42 in combination with increased T-tau and P-tau concentrations (96).

Findings from a small clinical study indicated a potential link between reduced levels of CSF T-tau and P-tau and suicidal ideation in individuals with MCI who were considered at risk of developing Alzheimer's disease, compared to healthy controls (94). The relationship between amyloid accumulation, tau pathology, and suicidal behavior has not been previously investigated in population-based cohorts.

BRAIN MORPHOLOGY VISUALIZED BY MRI AND SUICIDAL BEHAVIOR

White matter lesions (WML) are indicators of small vessel disease and impaired neural connectivity (Figure 5) (97), and have been consistently linked to cognitive decline and challenges in emotional regulation (98). A prior meta-analysis found that individuals with mood disorders and a history of suicide attempts typically exhibit a greater WML burden compared to those without

such a history (99). The association between WML volume and suicidal ideation, as opposed to suicide attempts, has not been previously explored.

The amygdala, a key structure involved in emotional regulation and cognitive processes such as decision-making (100) has been examined in clinical populations with a history of suicide attempts, though findings have been inconsistent (101-104). The amygdala had not yet been investigated in population-based samples.

The hippocampus, which is essential for relational memory reconstruction, flexible cognition, and decision-making (105) has been studied solely in individuals with a history of suicide attempts. However, the findings across these studies have been inconsistent (102, 104, 106, 107).

The parahippocampus is a region implicated in contextual memory and affect regulation (108), remains unexamined in relation to suicidal ideation, despite its functional relevance and proximity to other limbic structures.

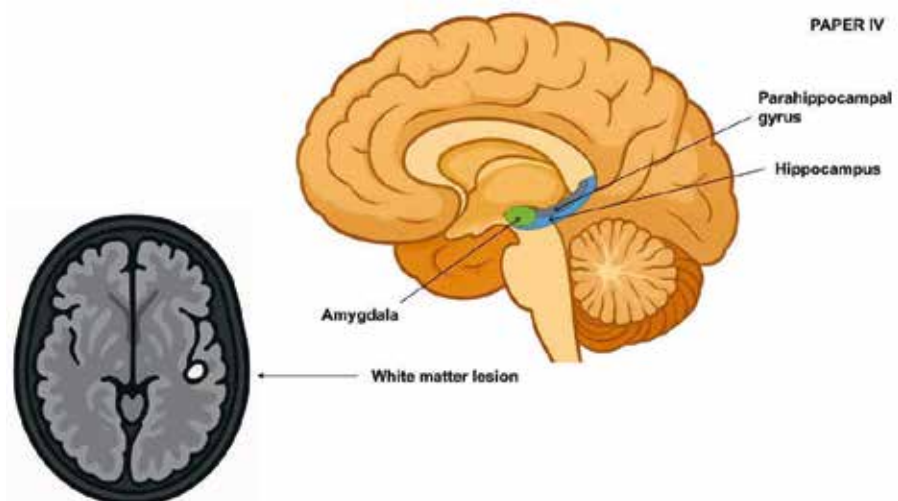


Figure 5. Illustration of an axial MRI brain section (left) highlighting a white matter lesion, alongside a sagittal view of key structures (right), including the amygdala, hippocampus, and parahippocampal gyrus. Original by the author.

AIM

The overall aim of this thesis was to explore neurobiological and cognitive factors associated with suicidal ideation in population-based cohorts of older adults. The specific aims were:

PAPER I

To assess whether CSF levels of YKL-40, GAP-43, and MBP—biomarkers indicative of neuroinflammation (YKL-40), synaptic plasticity and function (GAP-43), and myelin integrity (MBP), respectively—are associated with suicidal ideation.

PAPER II

To investigate the relationship between MCI and reports of suicidal ideation.

PAPER III

To investigate whether CSF levels of Ng and NfL, biomarkers of synaptic dysfunction and neuroaxonal damage respectively, are associated with suicidal ideation.

PAPER IV

To investigate whether differences in brain morphology—specifically WML volume and grey matter volumes of the amygdala, hippocampus, and parahippocampus—are associated with suicidal ideation.

PARTICIPANTS AND METHODS

Study cohorts were collected from two population-based studies, the Prospective Population Study of Women (PPSW) and the H70 Birth Cohort Studies (H70). Samples are described in Table 1.

Table 1. Study samples. Original by the author.

	Participants, n	Female n (%)	Male n (%)	Age (mean, SD)
Paper I	86	86 (100)	-	72.5 (3.3)
Paper II	916	692 (75.5)	224 (24.5)	74.0 (5.3)
Paper III	316	151 (47.8)	165 (52.2)	70.6 (0.3)
Paper IV	774	404 (52.2)	370 (47.8)	70.5 (0.3)

SD, Standard deviation

ETHICAL CONSIDERATIONS

All studies were approved by the Ethics Committee for Medical Research at the University of Gothenburg, Sweden (ref S377-99 and S227-00). All research has been conducted in accordance with the Declaration of Helsinki of the World Medical Association (109) and its fundamental principle on the respect for the individual (Article 8), his or her right to self-determination and the right to make informed decisions (Articles 20, 21 and 22) regarding participation in research, both initially and throughout the course of the research.

To provide informed consent, all study participants received written and oral study information and ensured time for eventual questions. Study participants were informed of their right to withdraw consent at any point during the study, without the need to provide a reason. The possible benefits of study participation is the thorough physical and mental examination. Participants were also referred to relevant specialist care in the event of detected pathological findings.

PARTICIPANTS

PAPER I

The study sample was drawn from the Prospective Population Study of Women (PPSW), a large-scale, population-based study initiated in 1968–1969 in Gothenburg, Sweden. This survey included a representative cohort of 1462 women (response rate: 90.1%) who were identified through the Swedish Population Register and were living in Gothenburg, Sweden, either in private homes or in residential care. Participants were born in the years 1908, 1914, 1918, 1922, and 1930 (110). Our study was based on the follow-up conducted in 1992–1993, which included 837 surviving women from the initial cohort who were invited to participate. Of these, 591 agreed to take part (response rate: 70.6%). Among them, 88 women aged 70–84 years consented to undergo a lumbar puncture (LP) procedure. Two individuals were subsequently excluded due to a dementia diagnosis at the time of the LP, resulting in a final sample of 86 non-demented women.

PAPER II

The study sample was drawn from the PPSW (110) and from the year 2000 cohort of the Gothenburg H70 Birth cohort study (111), a large epidemiological study focused on examining the health of older adults living in Gothenburg, Sweden. Participants were recruited from the Swedish Population Register and were residing either in private households or in residential care facilities. The sample included women from the PPSW born in 1908, 1914, 1918, and 1922, as well as women and men from the H70 cohort born in 1930. Among the 1504 individuals invited to participate in the psychiatric evaluation, 1018 agreed to take part, yielding a response rate of 67.7%. After excluding 94 individuals diagnosed with dementia, three with incomplete cognitive assessments, and five with missing data on suicidal ideation, the final study sample comprised 916 participants (692 women and 224 men).

PAPER III

The sample was drawn from the 2014 cohort of the Gothenburg H70 Birth Cohort Study (112), conducted between 2014 and 2016. Participants were selected from the Swedish Population Register and included 1839 women and men born in 1944 who were residing in either private homes or residential care facilities in Gothenburg. Of these, 1203 individuals (72.5% response rate)

consented to participate in the psychiatric examinations. Among them, 430 individuals agreed to undergo a LP. Medical contraindications to LP were identified in 108 participants, resulting in 322 individuals completing the procedure. Of these, five were excluded due to a dementia diagnosis and one due to incomplete data on suicidal ideation, yielding a final sample of 316 participants (151 women and 165 men).

PAPER IV

As in Paper III, the sample for this study was drawn from the 2014 cohort of the Gothenburg H70 Birth Cohort Study (112), with participant selection and study procedures identical to those described previously. A total of 788 individuals completed both MRI scans and assessments of suicidal ideation. After excluding 14 individuals diagnosed with dementia, the final analytical sample comprised 774 participants (404 women and 370 men).

PROCEDURES

Across Papers I–IV, a comprehensive series of clinical assessments was administered either at a geriatric outpatient clinic or within the participants' homes. These evaluations spanned multiple domains, including social, functional, physical, neuropsychiatric, and neuropsychological functioning.

In Paper II, additional clinical information was obtained through interviews with close informants to supplement participant data.

In Papers III–IV, data were collected on participants' lifetime history of depression.

In Papers I–IV, information was obtained regarding participants' history of stroke, educational level, smoking status, and cohabitation status.

Additionally, in Papers I–IV, data on current medication use was collected during the assessment and categorized according to the Anatomical Therapeutic Chemical (ATC) classification system..

INSTRUMENTS

In Papers I–IV, neuropsychiatric symptoms were assessed using the Comprehensive Psychopathological Rating Scale (CPRS) (23). Depressive

symptoms were evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) (23), a subscale of the CPRS, while cognitive function was screened using the Mini-Mental State Examination (MMSE) (113).

In Paper II, the MADRS score was calculated using a modified version consisting of seven items (MADRS-7), following the exclusion of two items: concentration difficulties and lassitude. These exclusions were made since concentration difficulties were used to assess cognitive status, while lassitude was excluded due to its overlap with the evaluation of suicidal ideation.

In Paper II, self-perceived cognitive function was assessed using selected items from the CPRS (Table 2) (23). In addition, Informant-based assessments were conducted through semi-structured interviews with a close informant, which included the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (114), which evaluates perceived cognitive changes over the previous ten years, independent of prior cognitive ability. The neuropsychiatric functioning was assessed using adapted elements from the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) (115). Basic activities of daily living (ADL) (116) were assessed based on the Katz Index (117) which determines the level of independence in the tasks of bathing, dressing, toileting, transferring, and feeding. Instrumental activities of daily living (IADL) including cleaning, shopping, using transportation, and cooking were also evaluated.

Alcohol use was assessed in Papers I–IV using the self-administered Alcohol Use Disorders Identification Test (AUDIT) (118), and participants' weekly alcohol consumption (grams per week) was estimated based on their reported drinking habits.

Source of information	Method and criteria	Assessed item
Participant	Personal perception rated on a 0–6 scale: <ul style="list-style-type: none"> • 0–2: No or mild issues • 3–6: Frequent or significant difficulties Impairment: score > 2	Memory difficulties Concentration difficulties Difficulties making decisions Difficulties taking initiative
Close informant	Close informant evaluates changes over the past 10 years on a scale from 1–5: <ul style="list-style-type: none"> • 1–2: Improved • 3: No change • 4–5: Declined Impairment: > weighted mean 3.125	Orientation to persons (3 items) Episodic recent memory (2 items) Working memory (1 item) Orientation to person (1 item) Orientation to time (1 item) Orientation to location (2 items) Know how to work familiar machines (1 item) Learning ability (2 items) Episodic remote memory (1 item) Semantic memory (2 items) Speech comprehension (1 item) Written language comprehension (1 item) Composing a letter (1 item) Adjusting ability (1 item) Ability to follow a story in a book or on TV (1 item) Making decisions (1 item) Handling money and finances (2 items) Abstract thinking (1 item) Reasoning ability item (1 item)
Neuropsychiatric examination	Professional rating on a 0-6 scale: <ul style="list-style-type: none"> • 0: No difficulties • 6: Severe difficulty Impairment: any score > 0	Memory Orientation to time Orientation to location Orientation to person Orientation to situation Recent memory Remote memory (2 items) Semantic memory (the three largest cities in Sweden; score range 0-3) Language Comprehension of spoken language Spoken language ability Word-finding difficulty Visuospatial ability Drawing geometrical figures Executive functioning Concentration Following commands Understanding proverbs (score range 0-4) Ideational praxis Word fluency (animals in 1 min)
Clinical self-care daily activity examination	Professional rating: independent or dependent Impairment: dependent	ADL Bathing Dressing Toileting Transferring Feeding IADL Cleaning Shopping Transportation Cooking

Table 2. Overview of assessment of cognitive function. Original by the author.

DIAGNOSIS

In Paper I-IV, major depression was diagnosed using criteria from the DSM-IV (119). The bereavement criterion was not applied, in order to align with DSM-5 (120) standards. A diagnosis required the presence of five or more depressive symptoms during the same two-week period, including either depressed mood or loss of interest or pleasure.

In Paper I, minor depression was identified using the DSM-IV research criteria, which required a persistently low mood or diminished interest or pleasure in most activities, along with a total of two to four additional symptoms.

In Paper I-IV, dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (121). The diagnostic process incorporated information from both neuropsychological testing and interviews with close informants, each assessed independently. A diagnosis of dementia required evidence of cognitive decline sufficient to interfere with social or occupational functioning and a minimum symptom duration of six months. Individuals who met these criteria were excluded from all analyses.

In Paper II, a total weekly alcohol consumption exceeding 100 g/week for women and 150 g/week for men was defined as current risk consumption.

ASSESSMENT OF SUICIDAL THOUGHTS AND BEHAVIORS

In Paper I, a score of 4 or higher on the suicidality item of the MADRS (23) was considered indicative of suicidal ideation within the past month.

In Papers II–IV, suicidal thoughts and behaviors were assessed using the Paykel questions (24), which include items addressing life-weariness, death wishes, thoughts of taking one's own life, serious contemplation of suicide, and suicide attempts, as previously described in the Introduction. Following the original classification by Paykel et al., responses were categorized according to time frames, differentiating between suicidal ideation experienced within the past year (last week, last month, or within the past year) and throughout an individual's lifetime (last week, last month, last year, or at any point more than a year ago).

In Paper IV, participants were also asked to report the age at which they first experienced each type of suicidal ideation or behavior.

CSF ANALYSIS

In Papers I and III, participants underwent a LP for CSF collection, typically performed in the morning following an overnight fast, through the L3/L4 interspace using standard sterile techniques. A total of 12 millilitres of CSF was drawn, gently mixed to prevent gradient effects, and promptly processed. The samples were centrifuged to eliminate cells and other insoluble materials, with minor differences in centrifugation parameters: 2000 g for 10 minutes at room temperature (20°C) in Paper I, and 1800 RCF for 10 minutes at 20°C in Paper III. The clear supernatant was then aliquoted into 1 ml portions, snap-frozen, and stored at -80°C (Paper I) or -70°C (Paper III) until analysis. All samples were transported under strict cold chain conditions to the Clinical Neurochemistry Laboratory at the University of Gothenburg. All biomarker analyses were conducted blinded to participants' clinical and psychiatric status.

CSF biomarkers were generally measured using various enzyme-linked immunosorbent assays (ELISAs) (122).

In Paper I, CSF YKL-40 concentrations were measured using the Human Chitinase 3-like 1 Quantikine ELISA Kit (R&D Systems, Minneapolis, MN), with an intra-assay coefficient of variation of 3.3%, an inter-assay coefficient of variation of 9.1%, and a detection limit of 6.25 ng/ml. CSF GAP-43 was determined at the detection limit of 140 pg/ml via sandwich ELISA (123), as previously described (124). CSF MBP levels were measured using the Active MBP ELISA Kit (Diagnostic Systems Laboratories Inc., Webster, TX) with a detection limit of 0.1 ng/ml.

In Paper III, CSF Ng was measured using a custom-developed ELISA test that were designed, optimized, and validated within the lab (in-house ELISA), which has been previously described (87). CSF levels of NfL were measured by sandwich ELISA (125). Sandwich ELISA was also used when measuring CSF levels of A β 42, T-tau, P-tau (126-128). The inter-assay coefficients of variation for the ELISA methods were 12% for A β 42, 10% for T-tau, and 9.8% for P-tau.

MCI DIAGNOSIS AND IMPAIRMENTS IN SPECIFIC COGNITIVE DOMAINS

MCI was defined according to the criteria established by Winblad et al, as described in the Introduction (95). An algorithm was used, which integrated binary (impaired/not impaired) data from the participant self-reports (115), interviews with a close informant (114), and neuropsychiatric evaluations (129) along with objective assessments of ADL (116) and IADL, as described in the Instruments section. Individuals without dementia were categorized as having MCI if they met the following conditions: 1) reported subjective cognitive decline (a score greater than 2 on any self-reported cognitive item), regardless of whether this was supported by the close informant (IQCODE score >3.12); 2) exhibited objective cognitive deficits in the neuropsychiatric assessment (score >0 on any cognitive item); and 3) maintained full independence in ADL and had only mild limitations in IADL (i.e., partial dependence, but not across all domains).

Participants who did not meet full MCI criteria but also could not be classified as cognitively intact (such as those with subjective complaints not corroborated by objective testing, or vice versa) were grouped as having cognitive impairment not meeting MCI criteria. To distinguish between cognitive and physical causes of functional limitations, research notes were reviewed when inconsistencies were found between cognitive performance and functional ability. Final MCI classification in such ambiguous cases was determined through consensus meetings among dementia specialists (SS, IS, SK). During these reviews, it was also agreed that functional impairments in participants with Mini-Mental State Examination (MMSE) scores above 26 were unlikely to be due to cognitive decline.

Among participants classified having MCI, impairments across the cognitive domains of memory, language, visuospatial skills, and executive function were evaluated using the neuropsychiatric assessment (see Table 2). All cognitive items were rated dichotomously (impaired/not impaired), and a single impaired score within a domain led to that domain being classified as impaired. Similarly, the categories of self-reported versus objectively measured cognitive impairment were determined based on their respective domains.

MRI EXAMINATIONS

Within three months of their initial study visit, participants were invited to undergo brain MRI scanning at the Aleris Clinic in Gothenburg, utilizing a 3.0 Tesla Philips Achieva scanner (112). WML volumes were assessed using version 2.0.15 of the Lesion Segmentation Tool (LST), an open-source toolbox integrated with the Statistical Parametric Mapping (SPM) platform (<https://www.fil.ion.ucl.ac.uk/spm/>). This tool is widely applied for the automatic segmentation of WMLs, which appear as hyperintensities in T2-weighted FLAIR images (130). To account for individual differences in brain size, WML volumes were normalized by total intracranial volume (ICV), estimated using the SPM12 software (112). WML measurements from thirteen participants did not meet quality control standards and were therefore excluded from the MRI analyses.

Grey matter regions of interest (ROIs) were quantified using the software FreeSurfer version 6.0.0 (<http://surfer.nmr.mgh.harvard.edu/>) via TheHiveDB platform (131). Mean volumes for the left and right hemispheres were calculated. Normalization was performed by adjusting each measured brain region volume in proportion to the participant's ICV, relative to the mean ICV of the study population. This was achieved by multiplying the individual brain region volume by the ratio of the population's average ICV to the participant's ICV.

STATISTICS

In Paper I, differences in mean CSF levels of YKL-40, GAP-43, and MBP were compared between participants with and without past-month suicidal ideation using Student's t-tests. To account for potential confounders, binary logistic regression models were used, adjusting for smoking status, BMI, and age, with results reported for fully adjusted models. Differences in biomarker levels across depression categories (no, minor, major) were assessed using F-tests, which test whether there are significant differences in means across multiple groups. Relationships between the CSF markers and individual MADRS items (excluding the suicide item) were initially tested using Fisher's exact test, followed by binary logistic regression with the same covariates.

In Paper II, group differences in continuous variables were compared using Student's t-test, while categorical variables were assessed using Fisher's exact test. The cognitively intact group served as the reference category for all comparisons. Stepwise backward logistic regression was applied to determine the association between cognitive status and suicidal ideation, with age, gender, marital status, education, and major depression included as covariates. Relationships between self-reported and objective cognitive deficits and suicidal ideation were examined using a fully adjusted regression model under the same covariates. Associations between impairments in specific cognitive domains and suicidal ideation were tested among individuals with MCI using Fisher's exact test and logistic regression models adjusted for age, sex, marital status, education, and major depression. In additional analysis, major depression was replaced with MADRS-7.

In Paper III, CSF Ng and NfL levels were dichotomized into "high" (highest quintile) and "low" (remaining quintiles) groups. CSF A β 42, T-tau, and P-tau levels were categorized as high or low using established thresholds (A β 42 \leq 530 pg/mL, T-tau \geq 350 pg/mL, P-tau \geq 80 pg/mL) (95). Ratios of CSF Ng to CSF A β 42, T-tau, and P-tau were also calculated. Fisher's exact test assessed categorical differences across the groups of high and low CSF Ng. Mann-Whitney U test was employed for continuous variables. Initial comparisons of suicidal ideation (past year and lifetime) between high and low CSF groups utilized Fisher's exact test with unadjusted odds ratios. Subsequent logistic regression models (stepwise backward) examined associations between high CSF Ng and lifetime suicidal ideation, adjusting for smoking, BMI, and self-

reported history of depression. Additional models tested the influence of low A β 42, high T-tau, and high P-tau as separate covariates.

In Paper IV, we compared WML volume and grey matter ROI volumes between participants with and without suicidal ideation using t-tests and Mann-Whitney U tests. Binary logistic regression models were used to test associations between MRI volumes and suicidal ideation, adjusting for sex, cohabitation, history of stroke, self-reported history of depression, and alcohol consumption. We also examined whether the timing of suicidal ideation onset (before or after age 40) was associated with neuroimaging variables.

All statistical tests across Paper I-IV were two-tailed, and significance was set at $p < 0.05$. Missing data was handled by list-wise deletion. Analyses were performed using SPSS for Windows, versions 17 through 29.

RESULTS

PAPER I

Eight participants reported experiencing suicidal ideation within the past month. These women exhibited higher MADRS scores compared to those without suicidal ideation, while MMSE scores did not differ between the groups. Additionally, CSF levels of YKL-40 and GAP-43 were higher among women report past month suicidal ideation, whereas CSF levels of MBP showed no difference between the two groups.

In the binary logistic regression models adjusted for smoking status, BMI, and age, both CSF levels of YKL-40 and GAP-43 remained associated with suicidal ideation (Table 3). Higher CSF YKL-40 levels were associated with suicidal ideation in the fully adjusted model. Additionally, a one-unit increase in CSF GAP-43 was associated with more than a fourfold increase in the odds of reporting suicidal ideation. In contrast, CSF MBP showed no association with suicidal ideation in any of the adjusted models.

	Smoking		BMI		Age		Fully adjusted		
	OR	CI (95%)	OR	CI (95%)	OR	CI (95%)	OR	CI (95%)	P
YKL-40 (10^{-8} g/ml)	1.15	1.01-1.30*	1.15	1.01-1.30*	1.12	1.00-1.25	1.17	1.02-1.34	0.026
GAP-43 (ng/ml)	3.42	1.07-11.01*	4.48	1.30-15.41*	3.22	0.97-10.69	4.61	1.29-16.49	0.019
MBP (ng/ml)	3.70	0.31-44.15	5.44	0.36-82.17	2.83	0.23-34.98	5.94	0.37-96.49	0.211

BMI, Body Mass Index. OR, Odds ratio. CI, Confidence interval.

* $P < 0.05$

Table 3. CSF markers in binary logistic regression models. Original by the author.

Major depression was diagnosed among 10 participants and minor depression in 9. No differences in YKL-40, GAP-43, or MBP levels were observed across the depression subgroups. Additionally, there was no relationship between CSF biomarker levels and depression severity, based on MADRS-stratified groups (no depression, mild, moderate).

The exploratory analyses examining associations between CSF biomarkers and individual MADRS items (excluding the suicide item) showed a relationship between higher CSF GAP-43 levels and feelings of worthlessness. This association remained after adjustment for smoking status, BMI, and age,

showing a nearly six-fold increase in odds ratio (OR 5.95 CI [1.52–23.20], $P = 0.01$). No associations were observed for YKL-40 or MBP in relation to any of MADRS items.

PAPER II

Among the participants, 182 individuals were diagnosed as cognitively intact, 286 with MCI, and 448 individuals were found to have cognitive impairment not meeting MCI criteria.

The distribution of reports of suicidal ideation within the past year and over the lifetime is presented in Table 4. Participants with MCI reported life-weariness during the past year more often than those without cognitive impairment. A similar pattern was observed for death wishes reported in the past year. In total, 16.0% of participants with MCI endorsed some degree of suicidal ideation during the previous year, compared to only 1.1% in the cognitively intact group.

This difference represents a nearly 17-fold increased odds of suicidal ideation among participants with MCI. An elevated risk was also seen in the group with cognitive impairment not meeting MCI criteria, however, their odds were substantially lower than those observed in the MCI group.

Lifetime experiences of life-weariness were more common among participants with MCI, with approximately one-third reporting such feelings at some point in their lives, compared to about one-tenth of those without cognitive impairment. Similarly, reports of lifetime death wishes and suicidal ideation of any severity were more frequent among individuals with MCI. A similar trend was observed in those with cognitive impairment that did not meet MCI criteria.

When adjusting for demographic factors and major depression, MCI remained related to higher odds of both life-weariness and death wishes reported within the past year (Table 5). Additionally, individuals with MCI were nearly three times more likely to have experienced life-weariness at any point in their lives.

Suicidal ideation	Cognitively intact (n=182)		Not fulfilling MCI criteria (n=448)		MCI (n=286)	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	
Past year						
Life weariness	1 (0.6)	22 (5.8)	9.92 (1.33-74.20)*	39 (16.8)	32.33 (4.39-237.94)*	
Death wishes	2 (1.2)	13 (3.2)	2.68 (0.60-12.02)	26 (10.3)	9.34 (2.19-39.88)*	
Thought of taking your life	1 (0.6)	3 (0.7)	1.22 (0.13-11.84)	7 (2.6)	4.54 (0.55-37.24)	
Seriously considered taking your life	0 (0.0)	1 (0.2)	-	3 (1.1)	-	
Attempted to take your life	0 (0.0)	0 (0.0)	-	1 (0.4)	-	
<i>Suicidal ideation, any severity level</i>	2 (1.1)	27 (6.1)	5.81 (1.37-24.69)*	45 (16.0)	16.99 (4.07-70.98)*	
Lifetime						
Life weariness	22 (12.1)	1 (20.4)	1.86 (1.13-3.08)*	92 (32.3)	3.47 (2.08-5.77)*	
Death wishes	19 (10.4)	2 (11.6)	1.13 (0.65-1.97)	59 (20.6)	2.23 (1.28-3.88)*	
Thought of taking your life	14 (7.7)	34 (7.6)	0.99 (0.52-1.89)	27 (9.4)	1.25 (0.64-2.46)	
Seriously considered taking your life	9 (4.9)	18 (4.0)	0.81 (0.36-1.83)	17 (5.9)	1.22 (0.53-2.79)	
Attempted to take your life	3 (1.6)	11 (2.5)	1.50 (0.41-5.45)	11 (3.9)	2.40 (0.66-8.71)	
<i>Suicidal ideation, any severity level</i>	27 (14.8)		1.82 (1.15-2.90)*	102 (35.7)	3.18 (1.98-5.12)*	

MCI, Mild Cognitive Impairment. OR, Odds ratio. CI, Confidence interval.

Associations between cognitive status and suicidal ideation were assessed using Fishers's exact test and are significant at $P < .05$.

Missing information regarding past year suicidal feelings: Cognitively intact $n = 3$, Not fulfilling MCI criteria $n = 11$ and MCI $n = 11$.

Missing information regarding lifetime suicidal feelings: Not fulfilling MCI criteria $n = 11$.

* $P < 0.05$

Table 4. Associations between cognitive status and reports of suicidal ideation. Original by the author.

Additional models adjusting for MADRS-7 items showed that MCI remained associated with life-weariness, regardless of the timeframe.

Regression models exploring subjective and objective cognitive impairment in relation to passive suicidal ideation showed that subjective cognitive complaints were associated with both life-weariness and death wishes, regardless of when they occurred. In contrast, objective cognitive impairment was associated only with life-weariness reported in the past year.

Finally, among participants with MCI, impairments in specific cognitive domains were analysed. Both memory impairment and deficits in visuospatial ability were associated with life-weariness reported within the past year, as well as with lifetime experiences of life-weariness.

Variable	Past year suicidal ideation	
	Life weariness	Death wishes
	OR (95% CI)	OR (95% CI)
Age	0.96 (0.89-1.04)	0.97 (0.89-1.05)
Sex (female)	2.66(0.70-10.21)	7.24 (0.94-55.58)
Married or cohabiting	0.42 (0.19-0.97)*	0.74 (0.30-1.82)
Education beyond mandator	1.12 (0.48-2.62)	1.40 (0.57-3.42)
Major depression	14.97 (5.37-41.74)*	8.49 (3.18-22.68)*
MCI	18.32 (2.44-137.75)*	5.30 (1.19-23.64)*

Variable	Lifetime suicidal ideation	
	Life weariness	Death wishes
	OR (95% CI)	OR (95% CI)
Age	0.97 (0.92-1.01)	0.98 (0.93-1.03)
Sex (female)	1.45 (0.77-2.74)	1.41 (0.69-2.87)
Married or cohabiting	0.46 (0.29-0.75)*	0.47 (0.27-0.79)*
Education beyond mandator	1.66 (1.03-2.70)*	1.43 (0.84-2.44)
Major depression	8.40 (3.35-20.99)*	4.72 (2.07-10.76)*
MCI	2.90 (1.67-5.05)*	1.75 (0.97-3.18)

MCI, Mild Cognitive Impairment. OR, Odds ratio. CI, Confidence interval.

Associations between MCI and suicidal ideation in logistic regression models (stepwise backward) are significant at $P < 0.05$.

* $P < 0.05$.

Table 5. Logistic regression models adjusted for relevant covariates. Original by the author.

PAPER III

Among participants, life weariness during the past year was reported by 9 individuals, death wishes by 7, and thoughts of taking one's life by 5. In total, 9 individuals (2.8%) reported experiencing any level of suicidal ideation during the past year. No associations were found between reports of past-year suicidal ideation and high CSF levels of Ng, NfL, T-tau, P-tau, or low CSF A β 42.

Lifetime suicidal ideation of any severity was reported by 58 participants (18.4%) (Table 6).

Variable	Life weariness (n = 51)		Death wishes (n = 37)		Thoughts of taking your life (n = 25)		Seriously considered taking your life (n = 7)		Suicidal ideation, any severity level (n = 58)	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
High Ng	17 (33.3)	2.31 (1.19-4.48)*	14 (37.8)	2.70 (1.30-5.61)*	11 (44.0)	3.47 (1.49-8.08)*	2 (28.6)	1.49 (0.28-7.86)	18 (31.0)	2.06 (1.09-3.92)*
High NFL	12 (23.5)	1.18 (0.58-2.41)	9 (24.3)	1.19 (0.53-2.66)	6 (24.0)	1.15 (0.44-3.00)	2 (28.6)	1.40 (0.26-7.39)	12 (20.7)	0.97 (0.48-1.95)
Low Aβ ₄₂	7 (13.7)	0.48 (0.21-1.12)	8 (21.6)	0.93 (0.41-2.14)	6 (24.0)	1.07 (0.41-2.80)	2 (28.6)	1.56 (0.30-8.28)	8 (13.8)	0.4 (0.21-1.06)
High T-tau	21 (41.2)	1.50 (0.81-2.77)	16 (43.2)	1.62 (0.81-3.27)	12 (48.0)	1.97 (0.87-4.50)	3 (42.9)	1.51 (0.33-6.89)	23 (39.7)	1.40 (0.78-2.53)
High P-tau	5 (9.8)	1.80 (0.63-5.21)	5 (13.5)	2.81 (0.95-8.33)	3 (12.0)	2.22 (0.60-8.19)	0 (0)	-	5 (8.6)	1.52 (0.53-4.37)

Ng, Neurogranin. NFL, Neurofilament light chain. Aβ₄₂, Amyloid-β₁₋₄₂. T-tau, Total tau. P-tau, Phosphorylated tau. OR, Odds ratio. CI, Confidence interval.
 Data for suicide attempts not shown due to cells with fewer than 5 counts.
 Fisher's exact test was used to test for differences in proportions and unadjusted OR were computed.
 Differences were considered significant at $P < 0.05$ (two-tailed).
 High Ng: values in the top quintile. Low Aβ₄₂: ≤330 pg/mL. High T-tau: ≥350 pg/mL. High P-tau: ≥80 pg/mL.
 * $P < 0.05$

Table 6. CSF biomarkers by lifetime suicidal ideation. Original by the author.

A relationship was found between high CSF Ng and lifetime experiences of life-weariness, death wishes, thoughts of taking one’s life as well as any level suicidal ideation.

These associations persisted even after adjusting for smoking status, BMI, and self-reported lifetime depression in fully adjusted regression models (Table 7).

Variable	Life weariness (n = 51)	Death wishes (n = 37)	Thought of taking your life (n = 25)	Suicidal ideation, any severity level (n = 58)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Current smoker	2.58 (1.03-6.46)*	2.60 (0.92-7.35)	0.82 (0.17-4.00)	2.89 (1.19-7.02)*
BMI	1.05 (0.98-1.12)	1.01 (0.93-1.10)	0.98 (0.88-1.08)	1.06 (1.00-1.13)
Self-reported lifetime depression	1.86 (0.97-3.58)	2.76 (1.33-5.75)*	2.74 (1.16-6.46)*	1.46 (0.77-2.76)
High Ng	2.03 (1.01-4.11)*	2.26 (1.02-4.98)*	3.17 (1.31-7.65)*	1.98 (1.00-3.90)*

BMI, Body Mass Index. Ng, neurogranin. OR, Odds ratio. CI, Confidence interval.
 Associations between Ng and suicidal ideation in logistic regression models (stepwise backward) were considered significant at $P < 0.05$ (two-tailed).
 High Ng: values in the top quintile.

Table 7. Logistic regression models adjusted for relevant covariates. Original by the author.

High CSF Ng was linked to a more than twofold increase in the odds of reporting life-weariness and death wishes, and with a more than threefold increase in the odds of reporting thoughts of taking one’s life. In contrast, no

associations were observed between lifetime suicidal ideation and other biomarkers, including high NfL, low A β 42, high T-tau, or high P-tau.

Additional regression models, each individually adjusted for low A β 42, high T-tau, and high P-tau, confirmed that the association between high CSF Ng and suicidal ideation remained robust across these adjustments. Furthermore, a distinct association was identified between low A β 42 and lifetime reports of life-weariness.

PAPER IV

As this paper has not yet been published, this section will only provide a brief summary of the results.

Individuals who had seriously considered suicide at some point in their lives showed greater WML volume compared to those without such ideation. However, after adjusting for relevant covariates, including depression, no associations remained between WML volume and suicidal ideation, regardless of its severity or timeframes. Similarly, no differences in mean grey matter ROI volumes were observed between participants with and without suicidal ideation, regardless of timeframe. The age at onset of suicidal ideation was also not associated with differences in WML or grey matter ROI volumes.

DISCUSSION

PAPER I

In Paper 1, women who had experienced suicidal ideation within the past month had higher CSF levels of both YKL-40 and GAP-43 compared to those without such ideation. These associations persisted even after adjusting for potential covariates and could not be attributed to depression status.

Since YKL-40 has not been previously examined in relation to suicidal ideation or behavior, direct comparisons with existing research are thus challenging. Nevertheless, YKL-40 is a well-established biomarker of microglial activation and neuroinflammation (132), both of which are biological processes consistently associated with suicidal behavior in previous studies (39, 40).

GAP-43 has not been previously examined in non-clinical samples. Nevertheless, our findings indicate that elevated CSF GAP-43 levels are associated with reports of suicidal ideation within the past month, consistent with prior evidence of increased GAP-43 immunoreactivity observed in a postmortem study of depressed individuals who died by suicide (84). Given that GAP-43 is a marker of synaptic plasticity (133), these findings further support the hypothesis that neurobiological alterations affecting neuronal connectivity may contribute to suicidal behavior. However, contrasting evidence comes from another postmortem study of suicide completers, which reported reduced GAP-43 levels in a similar population (85). These conflicting results may be attributable to differences in the brain regions analysed, methodological variations, the timing of suicide relative to sample collection, or the presence of comorbid conditions.

CSF levels of MBP did not differ between participants with and those without suicidal ideation. This result contrasts with earlier postmortem findings in individuals with schizophrenia and depression who died by suicide (85). The absence of association in our sample may reflect limitations in statistical power or may indicate that myelin-associated changes are less relevant to suicidal ideation than to completed suicide.

Finally, the exploratory analyses revealed an association between higher CSF GAP-43 levels and reported feelings of worthlessness, a symptom that has previously been linked to future suicide attempts (134). Although we were

unable to apply corrections for multiple comparisons due to the limited sample size, this specific finding may represent a meaningful lead for further investigation, suggesting that certain affective symptoms may be more closely linked to the underlying neurobiological processes associated with suicidal behavior.

In conclusion, the findings of this study support the involvement of neuroinflammation and synaptic dysfunction in the neurobiology of suicidal ideation.

PAPER II

In Paper II, we found that experiences of life-weariness and death wishes, regardless of the timeframe of ideation, were more common among individuals with MCI when compared to cognitively intact individuals. These associations remained even after adjusting for covariates, including depression status.

We could not identify any previous population-based studies that addressed the association between MCI, defined using the Winblad et al. criteria (95), and suicidal ideation for comparison. While not directly comparable, a prospective cohort study using diagnostic criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the AD and Related Disorders Association (NINCDS-ADRDA) found no increased risk of suicide among older adults with MCI attending memory clinics (135). Similarly, a case-control study of older suicide attempters found no association between MCI, assessed using MMSE and diagnostic interviews, and suicidal ideation (136). These discrepancies may be attributable to several factors, including variations in diagnostic criteria, differences in study populations, and the severity of suicidal ideation or behavior being addressed across studies.

Furthermore, our findings also indicated a connection between self-perceived cognitive impairment and reports of passive suicidal ideation, regardless of the timeframe. We were unable to locate any prior studies that directly examined the differences between self-reported cognitive impairment and objectively measured cognitive impairment in relation to suicidal ideation. However, several studies have reported an increased incidence of death by suicide shortly after a dementia diagnosis (137, 138). The authors of these previous studies have attributed this phenomenon to a subjective awareness about the eminent

progress of cognitive decline, further loss of functional abilities, fear of losing independence, and anxiety about becoming a burden to others.

In our study, individuals with MCI who reported passive suicidal ideation exhibited impairments in both memory function and visuospatial abilities. Our assessment of memory function included items regarding recent and remote memory, semantic memory as well as time orientation. Consistent with our findings, a previous population-based study also reported that individuals with passive suicidal ideation in the past month exhibited impairments in time orientation (66). In line with our results, several previous clinical studies have also identified short-term and working memory deficits among depressed older suicide attempters (17, 61, 139, 140).

Reduced visuospatial abilities, evidenced by difficulties in drawing geometric figures, were also observed among participants with MCI who reported passive suicidal ideation. Although a previous clinical study has shown that suicide attempters tend to perform poorly on similar tasks (141), this is the first study to examine this association within a population-based context.

In this study, no relationship was found between suicidal ideation and language-related abilities—such as speech comprehension, speech production, and word-finding difficulties—which are functions linked to the phonological loop component of working memory. Notably, this area has not been previously explored in relation to suicidal ideation.

Unexpectedly, executive function impairments were not associated with suicidal ideation among participants with MCI. This contrasts with previous studies linking executive dysfunction to suicidal behavior, although those studies primarily focused on clinically depressed individuals (58-61, 142, 143), making direct comparisons challenging. Variations in assessment methods may also explain these differing findings.

To conclude, the findings from this study suggest a relationship between passive suicidal ideation and MCI when compared to cognitively intact peers, independent of depression status. The study also highlighted both self-perceived cognitive difficulties and objective cognitive impairments, particularly in the memory and visuospatial domains. These results underscore the importance of considering cognitive status when assessing suicide risk in older adults.

PAPER III

In Paper III, we found that high CSF Ng was related to lifetime reports of passive suicidal ideation among older adults. These associations remained after adjusting for potential covariates, including self-reported lifetime depression. Furthermore, the association was not influenced by CSF biomarkers of AD.

We found that high CSF Ng was associated with a two- to three-fold increased risk of reporting life-weariness, death wishes, thoughts of self-harm, and suicidal ideation at any level of severity. Although Ng has not been previously explored in the context of suicidal behavior, its established role in synaptic plasticity and function may offer a plausible explanation for this association (87). Furthermore, the findings from this study align with those of Paper I, which also demonstrated a connection between synaptic dysfunction and suicidal ideation in older adults. Ng is known to be expressed in the prefrontal cortex and hippocampus—brain regions critical for mood regulation, cognitive flexibility, and stress adaptation (86, 144). Synaptic dysfunction in these areas could contribute to maladaptive stress responses and difficulties in emotional regulation, ultimately increasing the risk of suicidal behavior.

Additionally, Ng is expressed in the amygdala and neocortex, which, together with the hippocampus, play key roles in learning and memory. The presence of microgliosis in the neocortex of individuals who died by suicide further supports the notion that synaptic impairment in these regions may contribute to suicidal tendencies by diminishing the capacity to cope with environmental stressors (86, 145, 146). This concept is consistent with findings from Paper II, which identified a link between cognitive impairment—particularly memory impairments—and passive suicidal ideation.

In our study, we also observed that the association between high CSF Ng and a history of lifetime suicidal ideation could not be explained by alterations in the AD biomarkers. However, low CSF A β 42 was detected among participants reporting lifetime experiences of life weariness. Notably, a substantial proportion of individuals with high CSF Ng levels also exhibited increased CSF T-tau and P-tau concentrations, suggesting that these findings may reflect early-stage neurodegeneration and impaired neuronal function commonly seen in AD. Consistent with this, previous research has indicated that CSF Ng may serve as a marker of impaired memory performance, potentially signaling cognitive decline that can occur prior to or independently of AD pathology (147).

We could not identify any previous population-based studies directly exploring the relationship between amyloid burden, tau pathology, and suicidal behavior for comparison. However, a smaller clinical study reported an association between lower CSF T-tau and P-tau levels and suicidal ideation in patients with MCI and probable AD, compared to healthy controls (148).

NfL has not been previously examined in relation to suicidal ideation in population-based, non-clinical samples. Nevertheless, our findings indicate no association between CSF NfL levels and reports of suicidal ideation within the past year or across the lifetime, suggesting that structural neuronal damage may not play a central role in the emergence of suicidal thoughts. This stands in contrast to recent clinical evidence reporting elevated serum NfL levels in individuals hospitalized following a suicide attempt (94). Notably, that sample consisted predominantly of young women diagnosed with depression and assessed during acute intoxication—both factors that may influence NfL levels and complicate direct comparisons (149, 150). Moreover, it is important to note that the study relied on the Geriatric Depression Scale (GDS-30), which does not include items specifically designed to assess suicidal ideation. These discrepancies may reflect differences in sample composition, clinical severity, timing of biomarker collection, or the biological impact of acute physiological stressors.

In conclusion, the findings from this study highlight synaptic dysfunction—rather than broad neurodegeneration or structural neuronal damage—as a key contributor to the biological underpinnings of passive suicidal ideation in aging populations.

PAPER IV

Paper IV did not identify any relationship between WML volume and suicidal ideation across different severity levels and timeframes when adjusted for key covariates, including depression. However, participants who had seriously contemplated suicide displayed a higher WML volume compared to those without such thoughts in the unadjusted model. Furthermore, no differences were identified regarding grey matter ROI volumes between individuals with and those without suicidal ideation, whether considering past-year or lifetime occurrences. Neither early-onset nor late-onset suicidal ideation showed any association with the evaluated WML or grey matter ROI volumes.

We could not find any previous population-based study on the relationship between WML burden and suicidal behavior for comparison. Findings from a clinical study of depressed adults aged 60 and older reported a greater WML burden among individuals with a history of suicide attempts within the past six months compared to those without such a history (151). Similarly, two additional studies in mixed-age clinical populations with mood disorders found increased WML volume among recent suicide attempters. These findings may suggest that WML burden is more closely associated with suicide attempts, rather than passive suicidal ideation. It is also important to note that previous studies have focused on clinical populations with affective disorders, in which WML burden is typically elevated and strongly linked to late-life depression—a known risk factor for suicidality (152). WMLs are also frequently observed in older adults (153) and are linked to cardiovascular conditions such as hypertension and diabetes (154). Considering the older age of our study population, the presence of WMLs may indicate a cumulative cerebrovascular burden, which could contribute to both cognitive and emotional instability, particularly in response to stress (155), thereby heightening susceptibility to suicidal behavior.

We did not find any differences in amygdala volume between individuals with and without suicidal ideation, aligning with several clinical studies that similarly did not observe amygdala alterations among depressed suicide attempters. However, two studies have reported increased amygdala volumes among suicide attempters in specific populations, one covering women with major depression (101) and the second individuals with schizophrenia (156). Notably, the sample sizes in these studies were limited.

Similarly, we observed no differences in hippocampal volumes between individuals with and without suicidal ideation. Similar findings have been reported in individuals with MDD who reported suicidal plans or attempts. However, two studies have identified smaller hippocampal volumes; one observed this reduction among depressed individuals with a history of suicide attempts compared to those without, and the other reported a similar decrease relative to healthy controls.

No differences in parahippocampal volume were observed between individuals with and without suicidal ideation. We found no previous research directly exploring the structural characteristics of the parahippocampus in relation to suicidality. However, results from a functional imaging study reported increased connectivity between the left habenula—known for its role in mood

regulation and aversive processing (157), and the right parahippocampus in suicide attempters compared to non-attempters (102). This finding may represent a promising lead for future research into the neural mechanisms underlying suicidal behavior.

Finally, we found no volumetric differences between early-onset and late-onset suicidal ideation. This finding suggests that suicidal ideation, regardless of age of onset, may be driven more by functional alterations in brain connectivity than by detectable structural changes in brain volume. It is also possible that the imaging technique used lacked the sensitivity to identify subtle volumetric differences.

To conclude, although no association was found between suicidal ideation, WML, and grey matter ROI volumes, the greater WML burden observed in individuals with serious suicidal thoughts in the unadjusted models may indicate compromised white matter integrity as a contributing factor in suicidal behavior.

STRENGTHS

The primary strength of the study lies in the use of population-based samples across all four papers, which enhances the external validity of the findings. Comprehensive neuropsychiatric examinations were consistently applied, providing robust assessments of both the occurrence and severity of cognitive impairments and suicidal ideation across various time periods. This methodological consistency ensures that the findings are both reliable and comparable across studies.

Another notable strength is the integration of multiple data sources. Beyond self-reported information, data were enriched by incorporating insights from close informant interviews, direct clinical assessments, as well as standardized psychiatric interviews.

The inclusion of biological measures, including CSF biomarkers and magnetic MRI, further strengthens the objectivity of the findings. These biomarkers were analysed using well-established laboratory techniques, and imaging data were normalized for intracranial volume, enhancing the precision and comparability of the results.

In addition, validated assessment tools were employed across the studies, such as the Paykel questions for assessing suicidal ideation, which captured both passive and active suicidal thoughts. This standardized approach ensures the reliability of the measurements across different cohorts.

LIMITATIONS

Limitations of Study I-IV include the cross-sectional setting and thus, no causal inferences can be drawn about the relationship between biological changes and suicidal ideation. The relatively small number of individuals with severe suicidal ideation limits the ability to detect associations specific to more severe states of suicidal ideation.

Potential selection bias must also be considered, as individuals who agreed to participate in the studies in general and especially, in the additional examinations of LP or MRI, differed in their basic characteristics compared to those declining participation. Such differences could impact the generalizability of the findings.

The findings may not be fully generalizable beyond older, community-dwelling Swedish adults. Furthermore, Study I included only female participants, which limits the generalizability of these findings to male populations.

Additionally, reliance on self-reported information remains a limitation, as it may be subject to recall bias.

CONCLUSION

This thesis investigated the neurobiological correlates of suicidal ideation in older adults through a comprehensive, multimodal approach, integrating CSF biomarker analyses, neuropsychiatric assessments, and neuroimaging.

Across the four studies, the findings indicated that neuroinflammatory processes, synaptic dysfunction, cognitive impairment, and compromised white matter integrity may contribute to the vulnerability of suicidal ideation in later life.

Notably, both inflammatory and synaptic CSF markers, as well as cognitive impairment—including MCI subjective cognitive decline, and deficits in memory and visuospatial abilities—were associated with passive suicidal ideation independent of depression status. These findings suggest that the observed relationships extend beyond what can be attributed to depression alone.

Notably, both inflammatory and synaptic markers in CSF were associated with passive suicidal ideation, and where the relationship could not be explained by depression status, highlighting that biologically meaningful alterations may occur even in the absence of active suicidal thoughts or behaviors. Impaired cognitive competence in terms of MCI, subjectively perceived cognitive decline, and deficits in memory and visuospatial abilities were also identified as significant risk factors. An association between WML volume and serious suicidal ideation was observed in unadjusted analyses, while other structural brain measures showed no consistent correlation. This finding may indicate that biological changes associated with suicidal ideation primarily occur at a functional or molecular level, rather than being readily detectable through structural imaging.

A particularly important observation was that passive suicidal ideation, often considered less critical than active ideation, was associated with measurable neurobiological alterations. These alterations included changes in markers of synaptic dysfunction and inflammation, emphasizing that even passive thoughts may reflect significant underlying biological processes. However, the relatively small number of participants reporting severe or active suicidal ideation limits the ability to draw firm conclusions regarding biological differences between passive and active forms.

Finally, the thesis demonstrated the value of a multimodal research approach, combining CSF biomarker analysis, cognitive assessments, and neuroimaging. This approach allowed for a more integrated understanding of suicidal ideation in older adults, showing that neurobiological alterations associated with suicidal ideation are not limited to psychiatric symptoms but also involve objective physiological changes.

FUTURE PERSPECTIVES

Across all four studies, the cross-sectional design limits our ability to draw directional inferences, leaving unresolved whether elevated CSF biomarker levels represent enduring vulnerabilities (trait markers) or transient, state-dependent phenomena. To address this, future research should adopt longitudinal designs with larger, population-based cohorts and repeated assessments of CSF biomarkers, cognitive function, and their relation to suicidal behavior. Tracking these measures over time would help clarify how biomarker trajectories relate to the onset and progression of suicidal behavior.

Expanding the multimodal approach would also be beneficial in future research. Studies should aim to incorporate advanced techniques for measuring biomarkers in blood, employ novel neuroimaging methods, and integrate genetic data within the same cohort across longitudinal settings. Such an approach could provide a more comprehensive understanding of the biological underpinnings of suicidal behavior.

Finally, the complex interplay between neurobiological factors and psychosocial variables (e.g., early childhood adversity, stress exposure, and psychological endophenotypes) warrants further investigation. Future research should explore how these factors interact to influence suicidal ideation, integrating findings from multiple perspectives.

ACKNOWLEDGEMENT

I thank my main supervisor Simona Sacuiu for her patience and support throughout the highs and lows of this project. My co-supervisor Margda Waern for her expertise, guidance and thoughtful reviews. My co-supervisor Henrik Zetterberg for his enthusiasm and positive energy. My co-supervisor Ingmar Skoog for providing a conducive academic atmosphere.

I would like to express my deepest gratitude to Karina Stein, Head of Operations at the Addiction Disorders Clinic, Sahlgrenska University Hospital, for granting me the time and opportunity to carry out this project.

I thank the co-authors for their contribution to the studies included in this thesis: Silke Kern, Maria Bjerke, Kaj Blennow, Pia Gudmundsson, Eric Westman and Madeleine Mellqvist Fässberg.

I also thank Tom Marlow, Yadi Nejad and Valter Sundh statistical advice.

I extend my gratitude to all the participants of the H70 and PPSW who generously volunteered their time and contributed to this study.

All members of the Sahlgrenska Suicide Studies and Epinep: Stefan Wiktorsson, Anna-Maria Nilsson, Sara Hed, Petter Olsson, Sabrina Doering, Malin Rex, Sophie Liljedahl, Mattias Jonson, Isak Erling, Tina Jacobsson, Lena Johansson, Jonas Molinder, Johan Skoog, Jessica Samuelsson, Jenna Najar, Felicia Ahlner, Anna Dittrich, Anna Zettergren, Isak Fredén Klenfeldt, XinXin Guo, Mats Ribbe, Cecilia Doshé, Kelly Rombauts and Agnes Wiberg.

I thank Frida Mårtensson for her tremendous support and encouragement. I also thank Oliva, Adeline, Zoe, Ann-Christin, and Gerhard Mårtensson, as well as Alexander Stensjö, for their kindness and friendship.

Finally, I want to express my endless love and unwavering devotion to my son, Alexander. Your presence is my greatest source of happiness, motivation and strength in life.

REFERENCES

1. World Health Organization. Suicide worldwide in 2019: global health estimates. World Health Organization 2021.
2. Public Health Agency of Sweden. Statistics on suicide in Sweden. Public Health Agency of Sweden; 2025.
3. De Leo D. Late-life suicide in an aging world. *Nature Aging.* 2022;2(1):7-12.
4. Duberstein PR, Conwell Y, Seidlitz L, Lyness JM, Cox C, Caine ED. Age and suicidal ideation in older depressed inpatients. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 1999;7(4):289-96.
5. Miret M, Nuevo R, Morant C, Sainz-Corton E, Jimenez-Arriero MA, Lopez-Ibor JJ, et al. Differences between younger and older adults in the structure of suicidal intent and its correlates. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2010;18(9):839-47.
6. McIntosh JL, Santos JF. Methods of suicide by age: sex and race differences among the young and old. *International journal of aging & human development.* 1985;22(2):123-39.
7. Canetto SS, Sakinofsky I. The gender paradox in suicide. *Suicide & life-threatening behavior.* 1998;28(1):1-23.
8. Mergl R, Koburger N, Heinrichs K, Székely A, Tóth MD, Coyne J, et al. What Are Reasons for the Large Gender Differences in the Lethality of Suicidal Acts? An Epidemiological Analysis in Four European Countries. *PloS one.* 2015;10(7):e0129062.
9. Kyung-Sook W, SangSoo S, Sangjin S, Young-Jeon S. Marital status integration and suicide: A meta-analysis and meta-regression. *Social Science & Medicine.* 2018;197:116-26.
10. Stephenson M, Prom-Wormley E, Lannoy S, Edwards AC. The temporal relationship between marriage and risk for suicidal ideation. *Journal of affective disorders.* 2023;343:129-35.
11. Rizk MM, Herzog S, Dugad S, Stanley B. Suicide Risk and Addiction: The Impact of Alcohol and Opioid Use Disorders. *Curr Addict Rep.* 2021;8(2):194-207.
12. Sjögren H, Eriksson A, Ahlm K. Alcohol and unnatural deaths in Sweden: a medico-legal autopsy study. *J Stud Alcohol.* 2000;61(4):507-14.
13. Lorant V, Kunst AE, Huisman M, Costa G, Mackenbach J. Socio-economic inequalities in suicide: a European comparative study. *The British journal of psychiatry : the journal of mental science.* 2005;187:49-54.

14. Phillips JA, Hempstead K. Differences in U.S. Suicide Rates by Educational Attainment, 2000-2014. *American journal of preventive medicine*. 2017;53(4):e123-e30.
15. Olshansky SJ, Antonucci T, Berkman L, Binstock RH, Boersch-Supan A, Cacioppo JT, et al. Differences in life expectancy due to race and educational differences are widening, and many may not catch up. *Health affairs (Project Hope)*. 2012;31(8):1803-13.
16. Van Hootehem A, Røgeberg O, Bratsberg B, Lyngstad TH. Correlation between cognitive ability and educational attainment weakens over birth cohorts. *Scientific reports*. 2023;13(1):17747.
17. Dombrovski AY, Butters MA, Reynolds CF, 3rd, Houck PR, Clark L, Mazumdar S, et al. Cognitive performance in suicidal depressed elderly: preliminary report. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2008;16(2):109-15.
18. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry*. 2011;68(10):1058-64.
19. Dong M, Wang SB, Li Y, Xu DD, Ungvari GS, Ng CH, et al. Prevalence of suicidal behaviors in patients with major depressive disorder in China: A comprehensive meta-analysis. *Journal of affective disorders*. 2018;225:32-9.
20. Dong M, Zeng LN, Lu L, Li XH, Ungvari GS, Ng CH, et al. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. *Psychological medicine*. 2019;49(10):1691-704.
21. De Leo D, Padoani W, Scocco P, Lie D, Bille-Brahe U, Arensman E, et al. Attempted and completed suicide in older subjects: results from the WHO/EURO Multicentre Study of Suicidal Behaviour. *International journal of geriatric psychiatry*. 2001;16(3):300-10.
22. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *The American journal of psychiatry*. 2007;164(7):1035-43.
23. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. *Acta psychiatrica Scandinavica Supplementum*. 1978(271):5-27.
24. Paykel ES, Myers JK, Lindenthal JJ, Tanner J. Suicidal feelings in the general population: a prevalence study. *The British journal of psychiatry : the journal of mental science*. 1974;124(0):460-9.
25. Abou Chahla MN, Khalil MI, Comai S, Brundin L, Erhardt S, Guillemain GJ. Biological Factors Underpinning Suicidal Behaviour: An Update. *Brain Sci*. 2023;13(3).

26. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem.* 2016;139 Suppl 2(Suppl 2):136-53.
27. Tastan B, Heneka MT. The impact of neuroinflammation on neuronal integrity. *Immunol Rev.* 2024;327(1):8-32.
28. Francesco DE, Vanessa C, Michele dA, Fabrizio A, Massimiliano Q, Annamaria C. Brain incoming call from glia during neuroinflammation: Roles of extracellular vesicles. *Neurobiology of Disease.* 2024;201:106663.
29. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduction and Targeted Therapy.* 2023;8(1):359.
30. Garland EF, Hartnell IJ, Boche D. Microglia and Astrocyte Function and Communication: What Do We Know in Humans? *Frontiers in neuroscience.* 2022;16:824888.
31. Chiarelli RA, Carvalho GA, Marques BL, Mota LS, Oliveira-Lima OC, Gomes RM, et al. The Role of Astrocytes in the Neurorepair Process. *Frontiers in Cell and Developmental Biology.* 2021;Volume 9 - 2021.
32. McNamara NB, Munro DAD, Bestard-Cuche N, Uyeda A, Bogie JFJ, Hoffmann A, et al. Microglia regulate central nervous system myelin growth and integrity. *Nature.* 2023;613(7942):120-9.
33. Giovannoni F, Quintana FJ. The Role of Astrocytes in CNS Inflammation. *Trends Immunol.* 2020;41(9):805-19.
34. Malabendu J, Susanta M, Arundhati J, Kalipada P. Induction of IL-2 by interleukin-12 p40 homodimer and IL-12, but not IL-23, in microglia and macrophages: Implications for multiple sclerosis. *Cytokine.* 2024;174:156457.
35. Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS. Exploring the Role of Neuroplasticity in Development, Aging, and Neurodegeneration. *Brain Sci.* 2023;13(12).
36. Bruno A, Dolcetti E, Rizzo FR, Fresegna D, Musella A, Gentile A, et al. Inflammation-Associated Synaptic Alterations as Shared Threads in Depression and Multiple Sclerosis. *Frontiers in cellular neuroscience.* 2020;14:169.
37. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. *Signal Transduction and Targeted Therapy.* 2023;8(1):267.
38. Licinia G, Hanga CG, Sebastian C-T, Zahra B, Thomas BC, Xinguo R, et al. Relationships between inflammatory markers and suicide risk status in major depression. *Journal of psychiatric research.* 2021;134:192-9.
39. Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of Inflammation in Suicide: From Mechanisms to Treatment. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2017;42(1):271-83.

40. Brundin L, Erhardt S, Bryleva EY, Achtyes ED, Postolache TT. The role of inflammation in suicidal behaviour. *Acta psychiatrica Scandinavica*. 2015;132(3):192-203.
41. Dieperink E, Ho SB, Tetrick L, Thuras P, Dua K, Willenbring ML. Suicidal ideation during interferon-alpha2b and ribavirin treatment of patients with chronic hepatitis C. *General hospital psychiatry*. 2004;26(3):237-40.
42. Janssen HL, Brouwer JT, van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *Journal of hepatology*. 1994;21(2):241-3.
43. Lindqvist D, Janelidze S, Erhardt S, Traskman-Bendz L, Engstrom G, Brundin L. CSF biomarkers in suicide attempters--a principal component analysis. *Acta psychiatrica Scandinavica*. 2011;124(1):52-61.
44. Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biological psychiatry*. 2009;66(3):287-92.
45. Janelidze S, Mattei D, Westrin A, Traskman-Bendz L, Brundin L. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. *Brain, behavior, and immunity*. 2011;25(2):335-9.
46. Gonçalves de Andrade E, González Ibáñez F, Tremblay M. Microglia as a Hub for Suicide Neuropathology: Future Investigation and Prevention Targets. *Frontiers in cellular neuroscience*. 2022;16:839396.
47. Suzuki H, Ohgidani M, Kuwano N, Chrétien F, Lorin de la Grandmaison G, Onaya M, et al. Suicide and Microglia: Recent Findings and Future Perspectives Based on Human Studies. *Frontiers in cellular neuroscience*. 2019;13:31.
48. Tonelli LH, Stiller J, Rujescu D, Giegling I, Schneider B, Maurer K, et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta psychiatrica Scandinavica*. 2008;117(3):198-206.
49. Steiner J, Biela H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *Journal of psychiatric research*. 2008;42(2):151-7.
50. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain, behavior, and immunity*. 2014;42:50-9.
51. Schoenbaum G, Roesch MR, Stalnaker TA, Takahashi YK. A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature reviews Neuroscience*. 2009;10(12):885-92.

52. Greene JD, Sommerville RB, Nystrom LE, Darley JM, Cohen JD. An fMRI investigation of emotional engagement in moral judgment. *Science (New York, NY)*. 2001;293(5537):2105-8.
53. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in neurosciences*. 2000;23(10):475-83.
54. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends in cognitive sciences*. 2000;4(6):215-22.
55. Chudasama Y, Bussey TJ, Muir JL. Effects of selective thalamic and prelimbic cortex lesions on two types of visual discrimination and reversal learning. *European Journal of Neuroscience*. 2001;14(6):1009-20.
56. Ostlund SB, Balleine BW. Differential Involvement of the Basolateral Amygdala and Mediodorsal Thalamus in Instrumental Action Selection. *The Journal of Neuroscience*. 2008;28(17):4398-405.
57. Stufflebeam SM, Rosen BR. Mapping cognitive function. *Neuroimaging clinics of North America*. 2007;17(4):469-84, viii-ix.
58. Clark L, Dombrowski AY, Siegle GJ, Butters MA, Shollenberger CL, Sahakian BJ, et al. Impairment in risk-sensitive decision-making in older suicide attempters with depression. *Psychology and aging*. 2011;26(2):321-30.
59. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *The American journal of psychiatry*. 2001;158(5):735-41.
60. Westheide J, Quednow BB, Kuhn KU, Hoppe C, Cooper-Mahkorn D, Hawellek B, et al. Executive performance of depressed suicide attempters: the role of suicidal ideation. *European archives of psychiatry and clinical neuroscience*. 2008;258(7):414-21.
61. Richard-Devantoy S, Jollant F, Kefi Z, Turecki G, Olie JP, Annweiler C, et al. Deficit of cognitive inhibition in depressed elderly: a neurocognitive marker of suicidal risk. *Journal of affective disorders*. 2012;140(2):193-9.
62. Larson EB, Heinemann AW. Rasch analysis of the Executive Interview (The EXIT-25) and introduction of an abridged version (The Quick EXIT). *Archives of physical medicine and rehabilitation*. 2010;91(3):389-94.
63. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annual review of clinical psychology*. 2010;6:285-312.
64. Bunce D, Batterham PJ, Mackinnon AJ, Christensen H. Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. *Journal of psychiatric research*. 2012;46(12):1662-6.
65. Oh DJ, Han JW, Bae JB, Kim TH, Kwak KP, Kim BJ, et al. Executive dysfunction and risk of suicide in older adults: a population-based prospective cohort study. *Journal of neurology, neurosurgery, and psychiatry*. 2021;92(5):528-33.

66. Ayalon L, Litwin H. What cognitive functions are associated with passive suicidal ideation? Findings from a national sample of community dwelling Israelis. *International journal of geriatric psychiatry*. 2009;24(5):472-8.
67. Lara E, Olaya B, Garin N, Ayuso-Mateos JL, Miret M, Moneta V, et al. Is cognitive impairment associated with suicidality? A population-based study. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2015;25(2):203-13.
68. Vega JN, Newhouse PA. Mild cognitive impairment: diagnosis, longitudinal course, and emerging treatments. *Current psychiatry reports*. 2014;16(10):490.
69. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies. *Signal Transduction and Targeted Therapy*. 2024;9(1):211.
70. Valiukas Z, Tangalakis K, Apostolopoulos V, Feehan J. Microglial activation states and their implications for Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*. 2025;12(1):100013.
71. Gulisano W, Maugeri D, Baltrons MA, Fà M, Amato A, Palmeri A, et al. Role of Amyloid- β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. *Journal of Alzheimer's Disease*. 2018;64(s1):S611-S31.
72. Pless A, Ware D, Saggi S, Rehman H, Morgan J, Wang Q. Understanding neuropsychiatric symptoms in Alzheimer's disease: challenges and advances in diagnosis and treatment. *Frontiers in neuroscience*. 2023;17:1263771.
73. Jollant F, Guillaume S, Jaussent I, Castelnau D, Malafosse A, Courtet P. Impaired decision-making in suicide attempters may increase the risk of problems in affective relationships. *Journal of affective disorders*. 2007;99(1-3):59-62.
74. Conejero I, Navucet S, Keller J, Olié E, Courtet P, Gabelle A. A Complex Relationship Between Suicide, Dementia, and Amyloid: A Narrative Review. *Frontiers in neuroscience*. 2018;Volume 12 - 2018.
75. Haw C, Harwood D, Hawton K. Dementia and suicidal behavior: a review of the literature. *International psychogeriatrics*. 2009;21(3):440-53.
76. Conejero I, Navucet S, Keller J, Olié E, Courtet P, Gabelle A. A Complex Relationship Between Suicide, Dementia, and Amyloid: A Narrative Review. *Frontiers in neuroscience*. 2018;12.
77. Kvartsberg H, Duits FH, Ingelsson M, Andreasen N, Öhrfelt A, Andersson K, et al. Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's

disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2015;11(10):1180-90.

78. Craig-Schapiro R, Perrin RJ, Roe CM, Xiong C, Carter D, Cairns NJ, et al. YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. *Biological psychiatry*. 2010;68(10):903-12.

79. Bonnef-Barkay D, Wang G, Starkey A, Hamilton RL, Wiley CA. In vivo CHI3L1 (YKL-40) expression in astrocytes in acute and chronic neurological diseases. *Journal of neuroinflammation*. 2010;7:34.

80. Nemes AD, Ayasoufi K, Ying Z, Zhou Q-G, Suh H, Najm IM. Growth Associated Protein 43 (GAP-43) as a Novel Target for the Diagnosis, Treatment and Prevention of Epileptogenesis. *Scientific reports*. 2017;7(1):17702.

81. Routtenberg A, Cantalops I, Zaffuto S, Serrano P, Namgung U. Enhanced learning after genetic overexpression of a brain growth protein. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;97(13):7657-62.

82. Aigner L, Arber S, Kapfhammer JP, Laux T, Schneider C, Botteri F, et al. Overexpression of the neural growth-associated protein GAP-43 induces nerve sprouting in the adult nervous system of transgenic mice. *Cell*. 1995;83(2):269-78.

83. Allegra Mascaro AL, Cesare P, Sacconi L, Grasselli G, Mandolesi G, Maco B, et al. In vivo single branch axotomy induces GAP-43-dependent sprouting and synaptic remodeling in cerebellar cortex. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;110(26):10824-9.

84. Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ. Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience*. 1999;91(4):1247-55.

85. Hrdina P, Faludi G, Li Q, Bendotti C, Tekes K, Sotonyi P, et al. Growth-associated protein (GAP-43), its mRNA, and protein kinase C (PKC) isoenzymes in brain regions of depressed suicides. *Molecular psychiatry*. 1998;3(5):411-8.

86. Yilmaz A, Fuchs D, Price RW, Spudich S, Blennow K, Zetterberg H, et al. Cerebrospinal Fluid Concentrations of the Synaptic Marker Neurogranin in Neuro-HIV and Other Neurological Disorders. *Current HIV/AIDS reports*. 2019;16(1):76-81.

87. Portelius E, Zetterberg H, Skillbäck T, Törnqvist U, Andreasson U, Trojanowski JQ, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. *Brain : a journal of neurology*. 2015;138(Pt 11):3373-85.

88. Papuč E, Rejdak K. The role of myelin damage in Alzheimer's disease pathology. *Archives of Medical Science*. 2020;16(2):345-1.

89. Bjerke M, Zetterberg H, Edman A, Blennow K, Wallin A, Andreasson U. Cerebrospinal fluid matrix metalloproteinases and tissue inhibitor of metalloproteinases in combination with subcortical and cortical biomarkers in vascular dementia and Alzheimer's disease. *Journal of Alzheimer's disease : JAD.* 2011;27(3):665-76.
90. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, et al. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular psychiatry.* 2015;20(11):1266-85.
91. Zetterberg H. Neurofilament Light: A Dynamic Cross-Disease Fluid Biomarker for Neurodegeneration. *Neuron.* 2016;91(1):1-3.
92. Zetterberg H, Skillback T, Mattsson N, Trojanowski JQ, Portelius E, Shaw LM, et al. Association of Cerebrospinal Fluid Neurofilament Light Concentration With Alzheimer Disease Progression. *JAMA neurology.* 2016;73(1):60-7.
93. Dhiman K, Blennow K, Zetterberg H, Martins RN, Gupta VB. Cerebrospinal fluid biomarkers for understanding multiple aspects of Alzheimer's disease pathogenesis. *Cellular and molecular life sciences : CMLS.* 2019;76(10):1833-63.
94. Ramezani M, Simani L, Fard MG, Abbaszadeh F, Shadnia S. Increased levels of neurofilament light chain in suicide attempters' serum. *Translational neuroscience.* 2022;13(1):218-23.
95. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine.* 2004;256(3):240-6.
96. Andreasen N, Minthon L, Davidsson P, Vanmechelen E, Vanderstichele H, Winblad B, et al. Evaluation of CSF-tau and CSF-Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. *Archives of neurology.* 2001;58(3):373-9.
97. Kim JJ, Young SE, J. KJ, Young SE, and Kosten TA. Stress effects in the hippocampus: Synaptic plasticity and memory. *Stress.* 2006;9(1):1-11.
98. Launer LJ. Epidemiology of White-Matter Lesions. *International psychogeriatrics.* 2003;15:99-103.
99. Grangeon MC, Seixas C, Quarantini LC, Miranda-Scippa A, Pompili M, Steffens DC, et al. White matter hyperintensities and their association with suicidality in major affective disorders: a meta-analysis of magnetic resonance imaging studies. *CNS spectrums.* 2010;15(6):375-81.
100. Salzman CD, Fusi S. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annu Rev Neurosci.* 2010;33:173-202.

101. Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL, et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Molecular psychiatry*. 2007;12(4):360-6.
102. Gosnell SN, Velasquez KM, Molfese DL, Molfese PJ, Madan A, Fowler JC, et al. Prefrontal cortex, temporal cortex, and hippocampus volume are affected in suicidal psychiatric patients. *Psychiatry Res Neuroimaging*. 2016;256:50-6.
103. Duarte DGG, Neves MCL, Albuquerque MR, Turecki G, Ding Y, de Souza-Duran FL, et al. Structural brain abnormalities in patients with type I bipolar disorder and suicidal behavior. *Psychiatry Res Neuroimaging*. 2017;265:9-17.
104. Colle R, Chupin M, Cury C, Vandendrie C, Gressier F, Hardy P, et al. Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts. *Journal of psychiatric research*. 2015;61:13-8.
105. Rubin RD, Watson PD, Duff MC, Cohen NJ. The role of the hippocampus in flexible cognition and social behavior. *Front Hum Neurosci*. 2014;8:742.
106. Gifuni AJ, Ding Y, Olié E, Lawrence N, Cyprien F, Le Bars E, et al. Subcortical nuclei volumes in suicidal behavior: nucleus accumbens may modulate the lethality of acts. *Brain Imaging Behav*. 2016;10(1):96-104.
107. Rentería ME, Schmaal L, Hibar DP, Couvy-Duchesne B, Strike LT, Mills NT, et al. Subcortical brain structure and suicidal behaviour in major depressive disorder: a meta-analysis from the ENIGMA-MDD working group. *Translational psychiatry*. 2017;7(5):e1116.
108. Aminoff EM, Kveraga K, Bar M. The role of the parahippocampal cortex in cognition. *Trends in cognitive sciences*. 2013;17(8):379-90.
109. Association WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *Jama*. 2013;310(20):2191-4.
110. Bengtsson C, Blohme G, Hallberg L, Hallstrom T, Isaksson B, Korsan-Bengtson K, et al. The study of women in Gothenburg 1968-1969--a population study. General design, purpose and sampling results. *Acta medica Scandinavica*. 1973;193(4):311-8.
111. Karlsson B, Klenfeldt IF, Sigstrom R, Waern M, Ostling S, Gustafson D, et al. Prevalence of social phobia in non-demented elderly from a Swedish population study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2009;17(2):127-35.
112. Rydberg Sterner T, Ahlner F, Blennow K, Dahlin-Ivanoff S, Falk H, Havstam Johansson L, et al. The Gothenburg H70 Birth cohort study

- 2014-16: design, methods and study population. *European journal of epidemiology*. 2019;34(2):191-209.
113. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975;12(3):189-98.
114. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychological medicine*. 1989;19(4):1015-22.
115. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *The American journal of psychiatry*. 1984;141(11):1356-64.
116. Falk H, Johansson L, Ostling S, Thogersen Agerholm K, Staun M, Host Dorffinger L, et al. Functional disability and ability 75-year-olds: a comparison of two Swedish cohorts born 30 years apart. *Age and ageing*. 2014;43(5):636-41.
117. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *The Gerontologist*. 1970;10(1):20-30.
118. Bergman H KH, Rydberg U, Sandahl C. Audit. The alcohol use disorder identification test. A Swedish manual. Karolinska Institutet. 1994.
119. American Psychiatric Association. Washington D, USA: American Psychiatric Press; . *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. . 1994.
120. Maj M. Bereavement-related depression in the DSM-5 and ICD-11. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2012;11(1):1-2.
121. American Psychiatric Association. Washington, DC UAPP. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. 1987.
122. Tabatabaei MS, Ahmed M. Enzyme-Linked Immunosorbent Assay (ELISA). *Methods Mol Biol*. 2022;2508:115-34.
123. Hayrapetyan H, Tran T, Tellez-Corrales E, Madiraju C. Enzyme-Linked Immunosorbent Assay: Types and Applications. In: Matson RS, editor. *ELISA: Methods and Protocols*. New York, NY: Springer US; 2023. p. 1-17.
124. Sjögren M, Minthon L, Davidsson P, Granérus AK, Clarberg A, Vanderstichele H, et al. CSF levels of tau, β -amyloid1-42 and GAP-43 in frontotemporal dementia, other types of dementia and normal aging. *Journal of Neural Transmission*. 2000;107(5):563-79.
125. Gaetani L, Hoglund K, Parnetti L, Pujol-Calderon F, Becker B, Eusebi P, et al. A new enzyme-linked immunosorbent assay for neurofilament light in cerebrospinal fluid: analytical validation and clinical evaluation. *Alzheimer's research & therapy*. 2018;10(1):8.

126. Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Archives of neurology*. 1999;56(6):673-80.
127. Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Molecular and chemical neuropathology*. 1995;26(3):231-45.
128. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjögren M, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neuroscience letters*. 2000;285(1):49-52.
129. Sacuiu S, Sjogren M, Johansson B, Gustafson D, Skoog I. Prodromal cognitive signs of dementia in 85-year-olds using four sources of information. *Neurology*. 2005;65(12):1894-900.
130. Cedres N, Ferreira D, Machado A, Shams S, Sacuiu S, Waern M, et al. Predicting Fazekas scores from automatic segmentations of white matter signal abnormalities. *Aging*. 2020;12(1):894-901.
131. Muehlboeck JS, Westman E, Simmons A. TheHiveDB image data management and analysis framework. *Front Neuroinform*. 2014;7:49.
132. Yeo IJ, Lee CK, Han SB, Yun J, Hong JT. Roles of chitinase 3-like 1 in the development of cancer, neurodegenerative diseases, and inflammatory diseases. *Pharmacology & therapeutics*. 2019;203:107394.
133. Qiang Q, Skudder-Hill L, Toyota T, Wei W, Adachi H. CSF GAP-43 as a biomarker of synaptic dysfunction is associated with tau pathology in Alzheimer's disease. *Scientific reports*. 2022;12(1):17392.
134. Wakefield JC, Schmitz MF. Feelings of worthlessness during a single complicated major depressive episode predict postremission suicide attempt. *Acta psychiatrica Scandinavica*. 2016;133(4):257-65.
135. An JH, Lee KE, Jeon HJ, Son SJ, Kim SY, Hong JP. Risk of suicide and accidental deaths among elderly patients with cognitive impairment. *Alzheimer's research & therapy*. 2019;11(1):32.
136. Liu IC, Chiu CH. Case-control study of suicide attempts in the elderly. *International psychogeriatrics*. 2009;21(5):896-902.
137. Erlangsen A, Zarit SH, Conwell Y. Hospital-diagnosed dementia and suicide: a longitudinal study using prospective, nationwide register data. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2008;16(3):220-8.
138. Seyfried LS, Kales HC, Ignacio RV, Conwell Y, Valenstein M. Predictors of suicide in patients with dementia. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011;7(6):567-73.

139. Gujral S, Dombrovski AY, Butters M, Clark L, Reynolds CF, 3rd, Szanto K. Impaired Executive Function in Contemplated and Attempted Suicide in Late Life. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2013.
140. McGirr A, Dombrovski AY, Butters MA, Clark L, Szanto K. Deterministic learning and attempted suicide among older depressed individuals: cognitive assessment using the Wisconsin Card Sorting Task. *Journal of psychiatric research*. 2012;46(2):226-32.
141. Olsson P, Wiktorsson S, Sacuiu S, Marlow T, Ostling S, Fassberg MM, et al. Cognitive Function in Older Suicide Attempters and a Population-Based Comparison Group. *Journal of geriatric psychiatry and neurology*. 2016;29(3):133-41.
142. Dombrovski AY, Hallquist MN, Brown VM, Wilson J, Szanto K. Value-Based Choice, Contingency Learning, and Suicidal Behavior in Mid- and Late-Life Depression. *Biological psychiatry*. 2019;85(6):506-16.
143. Richard-Devantoy S, Szanto K, Butters MA, Kalkus J, Dombrovski AY. Cognitive inhibition in older high-lethality suicide attempters. *International journal of geriatric psychiatry*. 2015;30(3):274-83.
144. Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. *Molecular psychiatry*. 2020;25(3):530-43.
145. van der Zee EA, Luiten PG. Muscarinic acetylcholine receptors in the hippocampus, neocortex and amygdala: a review of immunocytochemical localization in relation to learning and memory. *Progress in neurobiology*. 1999;58(5):409-71.
146. Dixon ML, Thiruchselvam R, Todd R, Christoff K. Emotion and the prefrontal cortex: An integrative review. *Psychological bulletin*. 2017;143(10):1033-81.
147. Casaletto KB, Elahi FM, Bettcher BM, Neuhaus J, Bendlin BB, Asthana S, et al. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. *Neurology*. 2017;89(17):1782-8.
148. Ferrer-Cairols I, Montoliu T, Crespo-Sanmiguel I, Pulpulos MM, Hidalgo V, Gómez E, et al. Depression and Suicide Risk in Mild Cognitive Impairment: The Role of Alzheimer's Disease Biomarkers. *Psicothema*. 2022;34(4):553-61.
149. Li Z, Zhang J, Halbgebauer S, Chandrasekar A, Rehman R, Ludolph A, et al. Differential effect of ethanol intoxication on peripheral markers of cerebral injury in murine blunt traumatic brain injury. *Burns & trauma*. 2021;9:tkab027.
150. Sano T, Masuda Y, Yasuno H, Shinozawa T, Watanabe T, Kakehi M. Blood Neurofilament Light Chain as a Potential Biomarker for Central and Peripheral Nervous Toxicity in Rats. *Toxicological sciences : an official journal of the Society of Toxicology*. 2021;185(1):10-8.

151. Sachs-Ericsson N, Hames JL, Joiner TE, Corsentino E, Rushing NC, Palmer E, et al. Differences between suicide attempters and nonattempters in depressed older patients: depression severity, white-matter lesions, and cognitive functioning. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2014;22(1):75-85.
152. Kirton JW, Resnick SM, Davatzikos C, Kraut MA, Dotson VM. Depressive Symptoms, Symptom Dimensions, and White Matter Lesion Volume in Older Adults: A Longitudinal Study. *The American Journal of Geriatric Psychiatry*. 2014;22(12):1469-77.
153. Silverstone T, McPherson H, Li Q, Doyle T. Deep white matter hyperintensities in patients with bipolar depression, unipolar depression and age-matched control subjects. *Bipolar Disord*. 2003;5(1):53-7.
154. Gassner GM, Damestani NL, Wheeler NS, Kufer JA, Yadav SM, Mellen SF, et al. Cerebral microvascular physiology associated with white matter lesion burden differs by level of vascular risk in typically aging older adults. *J Cereb Blood Flow Metab*. 2024:271678x241300394.
155. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular psychiatry*. 2013;18(9):963-74.
156. Spoletini I, Piras F, Fagioli S, Rubino IA, Martinotti G, Siracusano A, et al. Suicidal attempts and increased right amygdala volume in schizophrenia. *Schizophr Res*. 2011;125(1):30-40.
157. Lawson RP, Nord CL, Seymour B, Thomas DL, Dayan P, Pilling S, et al. Disrupted habenula function in major depression. *Molecular psychiatry*. 2017;22(2):202-8.