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REGULAR ARTICLE

# Plasma neurofilament light chain in association to late-life depression in the general population

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**Aim:** Investigating what is underlying late-life depression is becoming increasingly important with the rapidly growing elderly population. Yet, the associations between plasma biomarkers of neuroaxonal damage and late-life depression remain largely unclear. Therefore, we determined cross-sectional and longitudinal associations of neurofilament light chain (NfL) with depression in middle-aged and elderly individuals, and total tau, β-amyloid 40 and 42 for comparison.

**Methods:** We included 3,895 participants (71.78 years [SD = 7.37], 53.4% women) from the population-based Rotterdam Study. Between 2002 and 2005, NfL, total tau, β-amyloid 40 and β-amyloid 42 were determined in blood and depressive symptoms were measured with the Center for Epidemiologic Studies Depression scale (CES-D). Incident depressive events (clinically relevant depressive symptoms, depressive syndromes, major depressive disorders) were measured prospectively with the Center for Epidemiologic Studies Depression, a clinical interview and follow-up of medical records over a median follow-up of 7.0 years (interquartile range 1.80). We used linear and Cox proportional hazard regression models.

**Results:** Each $\log_2$ pg./mL increase in NfL was cross-sectionally associated with more depressive symptoms (adjusted mean difference: 0.32, 95% CI 0.05–0.58), as well as with an increased risk of any incident depressive event over time (hazard ratio: 1.22, 95% CI 1.01–1.47). Further, more amyloid-β 40 was cross-sectionally associated with more depressive symptoms (adjusted mean difference: 0.70, 95% CI 0.15–1.25).

**Conclusion:** Higher levels of NfL are cross-sectionally associated with more depressive symptoms and a higher risk of incident depressive events longitudinally. The association was stronger for NfL compared to other plasma biomarkers, suggesting a potential role of neuroaxonal damage in developing late-life depression.

**Keywords:** *biomarkers, depression, middle aged, aged, neurology.*

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The elderly population is rapidly growing with expected tripling by 2050,[1] promoting healthy aging is therefore becoming increasingly important.[2] One common health issue in elderly individuals is late-life depression. Currently, the incidence rate of clinically relevant late-life-depressive symptoms is 6.8 per 100 person years[3,4]; for late-life major depressive disorder this is 2.3 per 100 person years.[3,5] Poor brain health might play an important role in the common occurrence of late-life depression. Evidence shows that those who suffer from neurodegenerative disease are more likely to experience late-life depression[6]: up to 29% of those with dementia develop a depressive disorder.[7,8] Additionally, neuroimaging markers, such as a smaller brain volume is associated with major depressive disorder late in life.[9] Together this may suggest that neurodegeneration or neuropathology may also increase the risk of having a depression later in life.

Several studies show that plasma biomarkers of neuropathology, such as β-amyloid 40 and β-amyloid 42, are associated with late-life depression.[10] A less studied biomarker in the context of late-life-depression is neurofilament light chain (NfL), which is a neuronal cytoplasmic protein that confers structural stability to neurons, with particularly high concentrations in dendrites, neuronal soma and axons.[11] NfL levels increase in cerebrospinal fluid and plasma proportionally to neuroaxonal damage[11]; higher NfL concentrations are found in plasma of patients with cognitive decline or neurodegenerative disease as compared to healthy controls.[11–13] As such, higher levels of NfL may reflect neuroaxonal damage or neuropathology, which can occur in the context of neurodegenerative disease,[11] but also in the context of brain aging or psychiatric disorders.[14,15] This makes NfL a sensitive marker for diffuse axonal damage, which can be a valuable addition to clinical and neuroimaging-related measures focusing on global structural neuronal damage (e.g., brain volume).[16]

Currently, cross-sectional associations of NfL with depressive symptoms and major depressive disorder have been reported in clinical samples. Two case control studies found higher levels of plasma NfL in middle-aged patients with major depressive disorder.[17,18] Additionally, in patients with Parkinson's Disease, NfL was associated with increased risk of depressive symptoms,[19] and in those with

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stroke NfL was associated with increased risk of major depressive disorder.[20] Yet, it remains unknown (i) whether these associations extend cross-sectionally to late-life depressive complaints in the general population, (ii) if there is a risk over time for developing incident depressive events, and (iii) how associations of NfL with depression compare to the associations of other more frequently investigated biomarkers (i.e., total tau, β-amyloid 40, and β-amyloid 42).

The current study examined whether plasma biomarkers for neuropathology associate with late-life depression in middle-aged and elderly individuals, based on data from the population-based Rotterdam Study. First, we assessed the cross-sectional association of NfL with depressive symptoms. Second, we investigated the longitudinal association of NfL with any depressive event (i.e., clinically relevant depressive symptoms, depressive syndromes, and major depressive disorders) as well as specifically major depressive disorder. Finally, we repeated analyses using other well-established plasma biomarkers of neuropathology (i.e., total tau, β-amyloid 40, and β-amyloid 42).

## Methods

### Setting and study population

The current study was conducted using data from the population-based Rotterdam Study cohort, which included participants from a district in Rotterdam, the Netherlands.[21] Participants were included in four subcohorts (RS-I, RS-II, RS-III, and RS-IV) from 1990 onwards in several waves, totaling 17,931 participants[21] aged 40 years and over. All participants were invited to undergo extensive examinations at study entry and subsequently every 3–6 years. More information on the study can be found elsewhere.[21]

The baseline to study associations of biomarker levels with depression symptoms was defined by the availability of −80°C stored plasma samples obtained from participants during the fourth visit of RS-I and the second visit of RS-II between 2002 and 2005 ($N = 6044$). These participants were followed up to measure incident depressive events until the occurrence of the first depressive event, death or end of follow-up (February 2012), whichever came first. Of these, 5,069 participants had sufficient plasma samples for determining biomarkers and informed consent to access medical records during follow-up. Additionally, we excluded the participants (i) with missing or invalid biomarker results ($N = 169$), (ii) without valid data on cross-sectional depressive symptoms and incident depressive events ($N = 150$), (iii) with any incident depressive event (i.e., clinically relevant depressive symptoms, depressive syndromes, major depressive disorder) up to 5 years prior to baseline ($N = 824$), (iv) with a bipolar disorder prior to baseline or during the study course ($N = 6$), and (v) with prevalent all-cause dementia at baseline ($N = 25$; see flowchart Supplemental Information Fig. S1). The final study sample included 3,895 participants.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The study conforms to the provision of the Declaration of Helsinki. The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831.

### Biomarkers (NfL, total tau, β-amyloid 40, and β-amyloid 42)

Venipuncture was performed between 8:00 and 10:30 AM after an overnight fast. Ethylene diamine tetra-acetic acid-treated containers were used to sample plasma. Plasma was centrifuged, aliquoted and frozen at −80 °C following standard procedures. Samples were assessed in two batches in 2018 through the Janssen Prevention Center (Leiden, Netherlands). Plasma was sent to the laboratory facilities of Quanterix (Lexington, MA, USA), using a single molecule array (Simoa) HD-1 analyzer platform.[22] NfL levels were measured with the Simoa NF-light® advantage kit.[23] Total tau, amyloid-β 40, and amyloid-β 42 levels were measured with the Simoa Human Neurology 3-Plex A assay (N3PA).[24] Two quality control samples were run on each plate for each biomarker. Samples were tested in duplicate, and if one or more were missing, the sample was excluded. We further excluded data if the concentration coefficient of variation exceeded 20%, or if control samples were out of range. For technical data on assay performance see De Wolf et al.[12]

### Depression

Depression was assessed in three ways. First, at baseline and during follow-up visits, depressive symptoms were measured with the validated Dutch version of the Center for Epidemiologic Studies-Depression (CES-D) scale.[25] The CES-D scale consists of 20 items that measure negative affect, lack of positive affect, interpersonal and somatic problems during the past week. Items are scored on a 4-point scale (0 = rarely or none of the time, 1 = some or a little of the time, 2 = occasionally or a moderate amount of the time, 3 = all of the time). A weighted total score was calculated if ≥75% of the questions were completed. If less questions were completed, CES-D scores were set to missing. A higher score indicates more depressive symptoms. Participants with a score ≥16 on the CES-D were classified as having clinically relevant depressive symptoms.[25]

Second, participants with a CES-D score ≥16 were invited for a semi-structured interview by a trained professional using the Dutch version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[26] Using this interview, participants were classified as having clinically relevant depressive symptoms, a depressive syndrome (i.e., mild depressive disorder or dysthymia) or major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th revised edition (DSM-IV-TR) criteria.

Third, in between baseline and follow-up, medical records were evaluated, which included data from general practitioner, specialist reports and hospital discharge letters. From these records, we retracted diagnoses of clinically relevant depressive symptoms, depressive syndromes and major depressive disorders according to DSM-IV-TR criteria.

To determine incident depressive events, we combined data on the first depressive event based on the CES-D, the SCAN interview and medical records (including clinically relevant depressive symptoms, depressive syndromes, and major depressive disorders).

### Other variables

As covariates, we included age, sex, education, paid employment, smoking, alcohol intake, body mass index (BMI), and estimated glomerular filtration rate (eGFR, i.e., assessment for overall kidney function[27]). Educational attainment was categorized using the UNESCO classification: (1) primary education, (2) lower intermediate (i.e., up to 3 years or less at secondary education or completed pre-vocational education), (3) intermediate-higher (i.e., more than 3 years of secondary education or completed vocational education), or (4) higher-university (completed higher professional education or university). Paid employment was defined as being in paid employment for ≥12 h per week. Smoking was categorized into never, former and current. Alcohol intake was calculated as grams per day. BMI was calculated as weight in kilograms divided by height in meters squared, as measured with calibrated scales at the research center. Finally, eGFR was calculated based on plasma creatinine,[28] which was acquired through the same venipuncture used to assess biomarkers.

### Statistical analyses

All analyses were performed using R version 4.0.0.[29] Missing values in covariates were handled with multiple imputations using chained equations (MICE),[30] with 30 imputation and 60 iterations. Given the

high missing value frequency of eGFR, we used eGFR from an earlier measurement round as auxiliary proxy variable in the imputation model. Biomarker concentrations were $\log_2$ transformed to approach normal distributions.

For our first aim, we assessed the cross-sectional association between NfL and depressive symptoms (i.e., CES-D scores) using linear regression models. Estimates reflect the adjusted mean difference in CES-D score per $\log_2$ pg./mL increase in biomarker concentrations. For our second aim, we assessed the longitudinal association between NfL and incident depressive events, using a Cox proportional hazard regression model. Follow-up time was defined as time between baseline and the occurrence of the first depressive event, death, or the end of follow-up. Estimates were elevated to an exponent and can be interpreted as hazard ratios, that is, the increase in risk of developing a depressive event per $\log_2$ pg./mL increase in biomarker concentration. Survival curves were used to visualize the time-to-event data, separately for participants with low (1 SD lower than the mean), average (within 1 SD lower and higher than the mean), and high (1 SD higher than the mean) concentrations of NfL. Survival curves were estimated using the Kaplan Meier function. The longitudinal associations were additionally assessed with only events of major depressive disorder as outcome. For our third aim, analyses were repeated with total tau, β-amyloid 40, and β-amyloid 42 as determinants and compared the results with NfL. Analyses were additionally rerun in standardized models, to enable comparison of effect sizes across different biomarkers.

All analyses were run in two adjustment models. The first model adjusted for age, sex and batch number of biomarker analysis. The second model additionally adjusted for education, paid employment, smoking, alcohol intake, BMI, and eGFR.

**Table 1.** Participant characteristics, shown for the total sample but also for the CES-D and incident data samples separately

| | Total sample ($N = 3895$) | | |
|---|---|---|---|
| Variable | M ± SD or Median [IQR] | *N* (%) | Missing *N* (%) |
| Age (years) | 71.78 ± 7.37 | | 0 (0.0) |
| Follow-up time | 7.03 [1.80] | | 99 (2.5) |
| Sex | | | 0 (0.0) |
| Men | | 1,816 (46.4) | |
| Women | | 2,079 (53.4) | |
| Education | | | 61 (1.6) |
| Low | | 401 (10.3) | |
| Middle | | 1,667 (42.8) | |
| Further | | 1,183 (30.4) | |
| High | | 583 (15.0) | |
| Paid employment | | | 5 (0.1) |
| Yes | | 3,649 (93.7) | |
| No | | 241 (6.2) | |
| Missing | | 5 (0.1) | |
| Smoking | | | |
| Never | | 1,145 (29.4) | |
| Former | | 1,118 (28.7) | |
| Current | | 1,632 (41.9) | |
| Alcohol (grams/day) | 12.38 ± 14.61 | | 0 (0.0) |
| BMI ($kg/m^2$) | 27.53 ± 3.98 | | 71 (1.8) |
| eGFR (mL/min) | 75.14 ± 14.75 | | 2,305 (59.2) |
| Developed dementia | | | 0 (0.0) |
| Yes | | 636 (16.3) | |
| No | | 3,259 (83.7) | |
| NfL ($\log_2$ pg./mL) | 3.77 ± 0.68 | | 46 (1.2) |
| Total tau ($\log_2$ pg./mL) | 1.26 ± 0.47 | | 135 (3.5) |
| Amyloid-β 40 ($\log_2$ pg./mL) | 8.02 ± 0.29 | | 161 (4.1) |
| Amyloid-β 42 ($\log_2$ pg./mL) | 3.34 ± 0.37 | | 283 (7.3) |
| Depressive symptoms CES-D (total score) | 3.94 ± 4.14 | | 0 (0.0) |

*Note*: Developed dementia shows participants that developed dementia during the study course (i.e., after biomarker assessment). BMI, body mass index; CES-D, center for epidemiologic studies-depression; eGFR, estimated glomerular filtration rate; NfL, neurofilament light chain.

## Results

### Population characteristics

The study population consisted of 3,895 participants (53.4% women) with an average age of 71.8 years (SD = 7.4) at venipuncture. Biomarkers were weakly to moderately correlated with each other (see Table S1). Participants had an average depressive symptom score of 3.94 (SD = 4.14) at baseline. Over the course of the study, 439 (11.3%) of the participants developed any depression, of which 51 (1.3%) developed a major depressive disorder. The median follow-up time was 7.0 years (interquartile range 1.80). See Table 1 for more details.

### Associations between NfL and depression

With each $\log_2$ pg./mL increase in NfL, participants reported a 0.32 (95% CI [0.05, 0.58]) points higher depressive symptoms score at baseline after adjustment for adjusted for age, sex, batch number, education, paid employment, smoking, alcohol intake, BMI, and eGFR (Table 2–Model 2). Additionally, with each $\log_2$ pg./mL increase in NfL, participants had a 22% (hazard ratio = 1.22, 95% CI [1.01, 1.47]) higher risk of developing any depressive event, and a 44% (hazard ratio = 1.44, 95% CI [0.86, 2.41]) higher risk of developing major depressive disorder, although the latter was not statistically significant (Table 3–Model 2). See Figure 1 for a graphical presentation.

**Table 2.** Cross-sectional association between biomarkers of neurodegenerative disease and depressive symptom

| | Cross-sectional depressive symptoms (CES-D) (Adjusted mean difference [95% CI]) | |
|---|---|---|
| Biomarker | Model 1 | Model 2 |
| Neurofilament light chain | 0.23 (0.00, 0.46) | 0.32* (0.05, 0.58) |
| Total tau | 0.16 (−0.11, 0.43) | 0.16 (−0.12, 0.44) |
| Amyloid-β 40 | 0.56* (0.08, 1.03) | 0.70* (0.15, 1.25) |
| Amyloid-β 42 | 0.14 (−0.21, 0.49) | 0.15 (−0.24, 0.53) |

*Note*: Adjusted mean difference = mean differences in CES-D score per $\log_2$ pg./mL increase in biomarker after adjustment for covariates; CES-D = Center for Epidemiologic Studies-Depression. Model 1 is corrected for age and sex. Model 2 is additionally correct for education, paid employment, smoking, alcohol intake, BMI, and eGFR.
*$P < 0.05$;

**Table 3.** Longitudinal association between biomarkers of neurodegenerative disease and incidence of depression

| Biomarker | Any depressive event Adjusted hazard ratio (95% CI) | | Major depressive disorder Adjusted hazard ratio (95% CI) | |
|---|---|---|---|---|
| | Model 1 | Model 2 | Model 1 | Model 2 |
| Neurofilament light chain | 1.15 (0.97, 1.37) | 1.22* (1.01, 1.47) | 1.28 (0.79, 2.08) | 1.44 (0.86, 2.41) |
| Total tau | 0.92 (0.75, 1.12) | 0.89 (0.72, 1.11) | 0.68 (0.37, 1.25) | 0.73 (0.39, 1.38) |
| Amyloid-β 40 | 1.16 (0.80, 1.71) | 1.23 (0.80, 1.90) | 1.41 (0.46, 4.31) | 2.31 (0.65, 8.24) |
| Amyloid-β 42 | 0.95 (0.73, 1.24) | 0.96 (0.72, 1.28) | 1.21 (0.55, 2.68) | 1.66 (0.68, 4.04) |

*Note*: Adjusted hazard ratio = hazard ratio, which can be interpreted as the increase in hazard per $\log_2$ pg./mL increase in biomarker concentration after adjustment for covariates; NfL, neurofilament light chain; Tau, total tau; AB40, amyloid-β 40; AB40, amyloid-β 42. Any depressive event includes clinically relevant depressive symptoms, depressive syndromes, and major depressive disorders. Model 1 is corrected for age and sex. Model 2 is additionally correct for education, paid employment, smoking, alcohol intake, BMI, and eGFR. A total of 439 (11.3%) participants had any depressive event, 51 (1.3%) had a major depressive event.
*$P < 0.05$;

Estimates in model 2 were comparable to estimates in model 1 (only corrected for age, sex and batch number), but the estimates in model 1 were not statistically significant.

### Associations between other biomarkers and depression

With each $\log_2$ pg./mL increase in amyloid-β 40, participants had a 0.70 (95% CI [0.15, 1.25]) points higher depressive symptoms score at baseline, after adjustment for age, sex, education, paid employment, smoking, alcohol intake, BMI, and eGFR (Table 2–Model 2). No other statistically significant cross-sectional or longitudinal associations were found. Estimates in model 2 were comparable to model 1 (only corrected for age, sex and batch number). Further, standardized adjusted estimates show that effect sizes were largest for the association of NfL with depressive symptoms cross-sectionally (see Table S2) and with any depressive event or a major depressive disorder over time (see Table S3), as compared to other biomarkers.

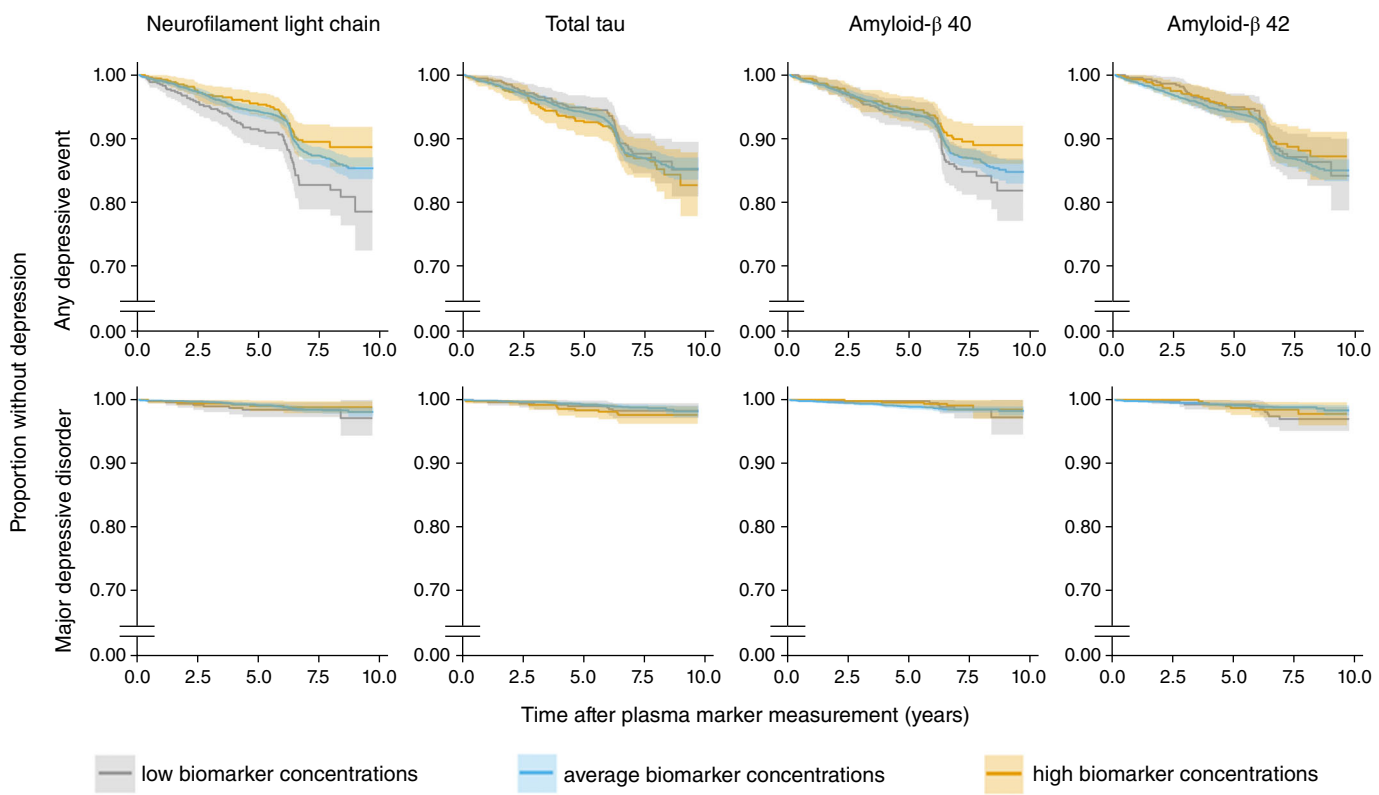


**Fig. 1** Survival curves for participants with different baseline levels of biomarkers. Low plasma marker concentrations represent levels equal to or less than 1 standard deviation below the mean, average plasma marker concentrations indicate levels within 1 standard deviation of the mean, high plasma markers represent levels equal to or higher than 1 standard deviation above the mean. Halfway through the follow-up period we observed a rapid decrease in the proportion of participants without depression, implying a steep increase in depression cases. This increase coincides with an examination round, reflecting the increased sensitivity of diagnosing depression with questionnaires and clinical interviews as opposed to using medical records.

## Discussion

In the current study, we demonstrated that NfL is associated with late-life depressive symptoms cross-sectionally, but also with an increased risk of having an incident depressive event over time, in a population-based setting of middle-aged and elderly persons. These associations were not found for total tau, β-amyloid 40, and β-amyloid 42 over time. Together, our findings suggest that neurofilament light chain is not only cross-sectionally linked to depression, but also increases the risk of having depression in the future within middle-aged and elderly individuals from the general population. This indicates a potential role of Nfl, a known biomarker for neuropathology and specifically neuroaxonal damage, as early biomarker for late-life depression.

The cross-sectional association between higher levels of NfL and more late-life depressive symptoms of this study support findings of previous case-control and patient studies for a link between neuroaxonal damage and late-life depression,[17–20] and extend this literature by providing evidence for associations in a population-based setting. This implies that associations emerge in clinical samples as well as in the elderly general population. We therefore conclude that the link between depression and NfL is not only apparent in those with more extreme NfL levels or more severe depression, but also across the full spectrum of NfL levels and depression.

Our longitudinal association showed that NfL is also an early marker for incident depressive events over time. Accordingly, we found that for each $\log_2$ pg./mL increase in NfL, participants had a 22% higher risk of developing any depressive event and – although not statistically significant – a 44% higher risk of developing major depressive disorder. These findings, indicating that neuroaxonal damage can be linked to subsequent late-life incident depressive events, are consistent with the current theory base. On the one hand, neuroaxonal damage may occur because of cerebrovascular disease (e.g., ischemic stroke[31]), which has been posited to predispose, precipitate, or perpetuate some geriatric depressive syndromes by the vascular depression hypothesis.[32] On the other hand, neuroaxonal damage may occur in the context of accelerated brain aging, which has been linked to psychiatric diseases.[14,15] Alternatively, neuroaxonal damage may be accompanied by inflammation of the neural system, which may contribute to depressive symptoms as posited by the inflammation hypothesis of late-life depression.[33] In accordance with all hypotheses, we could speculate that late-life incident depressive events may emerge because of neuroaxonal damage in circuity responsible for regulating emotions, such as the limbic-frontal circuitry.[34] Also, neuroaxonal damage is linked to preclinical changes in cognition and ultimately dementia risk,[12,13] which may contribute to the development of incident depressive events, for example through reduced engagement in leisure activities.[35] Overall, these findings suggest that prevention or remediation of neuroaxonal damage may be an interesting topic for follow-up research focused on alleviating late-life depression.

Yet, our results do not preclude that the association between neuroaxonal damage and depression could be reciprocal, exacerbating each other over time. A bidirectional association of NfL and depression could be speculated for example *via* an unhealthy lifestyle, reflected by more smoking, less physical activity, more drinking, and obesity.[36] These unhealthy life style factors can be both risk factors and consequences of depression,[37] and are also linked to neuroaxonal damage through increased oxidative stress.[38] Additionally, a reciprocal relationship between neuroaxonal damage and depression can be hypothesized through the bidirectional link between depression and neuroinflammation.[39] To further explore the potential reciprocal relationship between markers of neuroaxonal damage and depression, life-course models featuring repeated measures of NfL and depression are needed.

We also examined three other biomarkers of neuropathology in association with late-life depression. These biomarkers were less strongly associated with depression compared to NfL, although differences were relatively small. Our results confirm that total tau was not associated with late-life depression,[40] while higher plasma amyloid-β 40 was found to be associated with more late-life depressive symptoms.[10] Increased levels of amyloid-β 40 are typically linked to Alzheimer's disease pathology,[41] a neurodegenerative disease that is highly comorbid with late-life depression.[42] Moreover, major depressive disorder has been shown to increase the risk of developing Alzheimer's disease almost two-folds.[42] Yet, it needs to be noted that there is a considerable overlap in symptoms across these two disorders, such as, for example, low mood, lack of motivation, sleepiness, and subtle cognitive impairment.[43] To better understand the differences between depression, neurodegenerative disorders, and the role of neuropathology biomarkers, it will be important to disentangle whether associations between neuropathology biomarkers and late-life depression are different for participants that also develop dementia across as compared to those who stay free of dementia. Elevated levels of NfL could reflect Alzheimer's disease pathology rather than being directly related to depression. Unfortunately, our study design did not allow us to condition analyses on potential future dementia outcomes, thereby limiting our ability to fully understand the role of Alzheimer's disease as a confounding factor.

Of note, our results could also reflect differences in how NfL was measured as compared to other biomarkers. Different measurement arrays were used for NfL (Simoa NF-light® advantage kit) than for total tau, amyloid-β 40, and amyloid-β 42 levels (Simoa Human Neurology 3-Plex A assay (N3PA). Both arrays use plasma, but plasma measurements of total tau and amyloid-β 40 and 42 are typically less accurate due to the low concentrations of these proteins in blood and the difficulty in distinguishing between different forms of these proteins.[44] NfL, in contrast, has been considered a more reliable biomarker of neuropathology, as plasma levels of NfL have been shown to correlate well with cerebrospinal fluid levels of NfL.[44] Nonetheless, the current study suggests that the brain-related etiology underlying late-life depression may go beyond general neurodegeneration, as associations were most strong for a sensitive but unspecific marker for neuroaxonal damage,[11] posing NfL as a potential promising biomarker for late-life depression.

Our study has several strengths, including the use of data from a large, population-based sample and the prospective depression measurement which leveraged a combination of questionnaires, clinical interviews, and medical records. The results should, however, also be considered in the light of the following limitations. First, biomarkers for neurodegenerative disease were assessed through plasma with the Simoa NF-light® advantage kit add the Simoa Human Neurology 3-Plex A assay (N3PA). The Simoa platforms do not allow for establishing the origin of the biomarker (e.g., periphery or central nervous system). Studies that allow for measuring central nervous system-specific NfL (e.g., by assessment through cerebrospinal fluid), may be more precise.[45] Yet, earlier work in our cohort showed that NfL is associated to the risk of all-cause dementia,[12] which reflects that plasma biomarkers may validly indicate preclinical neurodegenerative disease. In addition, it might have been helpful to include additional biomarkers such as phosphorylated tau-181. While total tau serves as a general marker for neuronal damage, phosphorylated tau-181 is more specific to Alzheimer's pathology and could have provided a more nuanced understanding of the relationships under study.[46] Second, the sample consisted of middle-aged and elderly individuals from the general population, therefore, we may not have included individuals on the higher end of clinical symptoms (i.e., extreme levels of biomarkers, severe depression). Accordingly, effect estimates for major depressive disorder as outcome were large but not significant, potentially due to the low statistical power in these analyses; only 53 participants developed a major depressive disorder during the course of the study (1.3%). Larger samples (e.g., consortium studies) are required to identify effects with more confidence.

In summary, middle-aged and elderly individuals with higher plasma levels of NfL, a marker for more neuroaxonal damage[11] and known risk factor for neurodegenerative disease,[12] have more late-life

depressive symptoms, and ultimately a higher risk of incident depressive events over time. Potentially, neuroaxonal damage is an interesting intervention candidate for alleviating or preventing the development of late-life depressive symptoms. This study emphasizes that, beyond general neurodegeneration, neuroaxonal damage may have an important role in late-life depression, paving the way to a better understanding of etiological mechanisms underlying late-life depression.

## Author contributions

All authors were involved in conceptualization and methodology of the study and reviewing the original draft. IS was additionally involved in project administration, formal analyses, and writing the original draft. MG was additionally involved in data curation. CC and AI were additionally involved in supervision.

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## Disclosure statement

The authors disclose no conflicts of interest.

## Ethical approval registration

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The study conforms to the provision of the Declaration of Helsinki.

## Patient consent statement

All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

## Trial registration

The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831.

### Data availability statement

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.