Am J of Geriatric Psychiatry 32:9 (2024) 1141–1153

Available online at www.sciencedirect.com

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journal homepage: www.ajgponline.org

Regular Research Article

Depressive Symptoms and Plasma Markers of Alzheimer's Disease and Neurodegeneration: A Coordinated Meta-Analysis of 8 Cohort Studies

Emma L. Twait, Ph.D., Maria Kamarioti, M.Sc, Inge M.W. Verberk, Ph.D., Charlotte E. Teunissen, Ph.D., Astrid C.J. Nooyens, Ph.D., W.M. Monique Verschuren, Ph.D., Pieter Jelle Visser, Ph.D., Martijn Huisman, Ph.D., Almar A.L. Kok, Ph.D., P. Eline Slagboom, Ph.D., Marian Beekman, Ph.D., Dina Vojinovic, Ph.D., Nico Lakenberg, Ph.D., M. Arfan Ikram, Ph.D., Isabel K. Schuurmans, Ph.D., Frank J. Wolters, Ph.D., Justine E.F. Moonen, Ph.D., Lotte Gerritsen, Ph.D., Wiesje M. van der Flier, Ph.D., Mirjam I. Geerlings, Ph.D., On behalf of the NCDC Consortium

ARTICLE INFO

Article history:
Received September, 20 2023
Revised February, 22 2024
Accepted March, 6 2024

ABSTRACT

Background: *Depressive symptoms are associated with an increased risk of Alzheimer's disease (AD). There has been a recent emergence in plasma biomarkers for AD pathophysiology, such as amyloid-beta (Aβ) and phosphorylated tau (p-tau), as well as for axonal damage (neurofilament light, NfL) and*

From the Julius Center for Health Sciences and Primary Care (ELT, MK, WMMV, MIG), University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands; Amsterdam UMC, Location Vrije Universiteit (ELT), Department of General Practice, Amsterdam Public Health, Amsterdam Neuroscience, Amsterdam, The Netherlands; Neurochemistry Laboratory (IMWV, CET), Department of Laboratory Medicine, Amsterdam Neuroscience, Neurodegeneration, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands; National Institute for Public Health and the Environment (ACJN, WMMV), Bilthoven, The Netherlands; Alzheimer Center Amsterdam (PJV, JEFM, WMF), Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC Location VUmc, Amsterdam, The Netherlands; Department of Psychiatry and Neuropsychology (PJV), School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands; Amsterdam UMC Location Vrije Universiteit Amsterdam (MH, AALK, WMF), Epidemiology and Data Science, Amsterdam, The Netherlands; Department of Sociology, Faculty of Social Sciences (MH), Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; Amsterdam Public Health (MH, AALK), Ageing and Later Life, Amsterdam, The Netherlands; Molecular Epidemiology (PES, MB, DV, NL), Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands; Department of Epidemiology (DV, MAI, IKS, FJW), Erasmus University Medical Center, Rotterdam, Netherlands; Harvard T.H. Chan School of Public Health (MAI), Boston, MA; Department of Radiology & Nuclear Medicine (FJW), Erasmus MC, Rotterdam The Netherlands; Department of Psychology (LG) Utrecht University, Utrecht, The Netherlands; and the Amsterdam UMC (MIG), Location University of Amsterdam, Department of General Practice, Amsterdam Public Health, Amsterdam Neuroscience, Amsterdam, The Netherlands. Send correspondence and reprint requests to Mirjam I. Geerlings, Ph.D., Amsterdam UMC, Location University of Amsterdam, Department of General Practice, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands. e-mail: m.i.geerlings@amsterdamumc.nl

https://doi.org/10.1016/j.jagp.2024.03.004

Key Words:
Depression
biomarkers
dementia
late-life

astrocytic activation (glial fibrillary acidic protein, GFAP). Hypothesizing that depressive symptoms may occur along the AD process, we investigated associations between plasma biomarkers of AD with depressive symptoms in individuals without dementia. ***Methods:*** *A two-stage meta-analysis was performed on 2 clinic-based and 6 population-based cohorts (N = 7210) as part of the Netherlands Consortium of Dementia Cohorts. Plasma markers (Aβ42/40, p-tau181, NfL, and GFAP) were measured using Single Molecular Array (Simoa; Quanterix) assays. Depressive symptoms were measured with validated questionnaires. We estimated the cross-sectional association of each standardized plasma marker (determinants) with standardized depressive symptoms (outcome) using linear regressions, correcting for age, sex, education, and APOE ε4 allele presence, as well as subgrouping by sex and APOE ε4 allele. Effect estimates were entered into a random-effects meta-analysis.* ***Results:*** *Mean age of participants was 71 years. The prevalence of clinically relevant depressive symptoms ranged from 1% to 22%. None of the plasma markers were associated with depressive symptoms in the meta-analyses. However, NfL was associated with depressive symptoms only in APOE ε4 carriers (β 0.11; 95% CI: 0.05 −0.17).* ***Conclusions:*** *Late-life depressive symptoms did not show an association to plasma biomarkers of AD pathology. However, in APOE ε4 allele carriers, a more profound role of neurodegeneration was suggested with depressive symptoms.* (Am J Geriatr Psychiatry 2024; 32:1141−1153)

Highlights

- **What is the primary question addressed by this study?**
  The current study aimed to assess if late-life depressive symptoms were associated with plasma amyloid-beta42/40, p-tau181, neurofilament light, or glial fibrillary acidic protein.
- **What is the main finding of this study?**
  Late-life depressive symptoms were not associated with plasma biomarkers for Alzheimer's disease pathology, axonal injury, or astrocytic activation.
- **What is the meaning of the finding?**
  In those with a genetic risk for Alzheimer's disease, axonal injury was associated with increased depressive symptoms.

INTRODUCTION

Depression has been coined as one of the main risk factors for Alzheimer's disease (AD) dementia.[1–4] One longitudinal study in older adults found that with every increasing point on a depressive symptom scale, the risk of AD increased by 19%.[5] Another study found that high levels of depressive symptoms were associated with a 50% increased risk of dementia.[6] However, the mechanistic relationship between the two is not yet fully understood. Some studies have highlighted depression as a possible risk factor while others suggest that depression may in fact be an early manifestation of underlying AD.[7,8] These hypotheses may coexist and are not mutually exclusive. Late-life depressive symptoms and AD may have a common biological cause,[9,10] where depressive symptoms may indicate preclinical AD pathology.[7,11,12] Studying AD-related biomarkers associated with depressive symptoms may help entangle the pathophysiology of depressive symptoms in late-life.

Biomarkers related to AD pathology are amyloid-beta (Aβ) plaques and phosphorylated tau (p-tau).[13] These pathologies have thus far mostly been detected using position emission tomography (PET) scans[14] or in cerebrospinal fluid (CSF) obtained through a lumbar

puncture.[15] These methods are costly and invasive, hampering their wider application to the general population. Two other developing biomarkers, neurofilament light (NfL) (reflecting axonal damage) and glial fibrillary acidic protein (GFAP) (reflecting astrocyte activation), have also been suggested as biomarkers for AD-related pathological changes and can be assessed in CSF.[16–18]

While these markers have been validated for assessment in plasma,[19] studies assessing these plasma biomarkers with late-life depressive symptoms are scarce.[20] Regarding Aβ, a systematic review and meta-analysis found inconsistent results, with a higher plasma Aβ40/42 ratio (i.e., more Aβ burden) associated with depression, but no significant differences in CSF.[21] Thus far, no studies on plasma p-tau181 and depression have been done, only two cross-sectional studies using tau PET in individuals with major depressive disorder[22,23] and two longitudinal studies on depressive symptoms using CSF p-tau181,[24,25] which found higher tau burden also related to more depressive symptoms or depression diagnosis. Regarding the non-specific biomarkers, studies thus far have solely focused on the clinical diagnosis of depression, with higher levels of serum GFAP[26] and plasma NfL[27] found in those with major depressive disorder compared to those without major depressive disorder. Previous studies have highlighted the need for assessing the relationship between plasma AD pathophysiology and depression using ultrasensitive immunoassays,[28] such as Simoa, that have higher reliability of measuring both Aβ and tau levels, which occur in exponentially smaller quantities in plasma.[29]

Given the lack of current studies assessing depressive symptoms with AD-related pathophysiology in plasma, as well as in population-based settings, we aimed to assess the cross-sectional relationship between plasma Aβ42/40, p-tau181, NfL, and GFAP with depressive symptomology in the Netherlands Consortium for Dementia Cohorts (NCDC) including eight cohort studies of individuals without dementia.

METHODS AND MATERIALS

Study Design

This study incorporated a two-stage meta-analysis within the NCDC consortium. The NCDC consortium consists of nine prospective, Dutch cohort studies. Cohorts from the NCDC consortium were selected for the current study based on a number of criteria, including (1) availability of plasma markers, (2) assessment of depressive symptoms, and (3) no diagnosis of dementia.

The current study excluded two cohorts (i.e., Lifelines and the Maastricht Study), because those did not have data on plasma biomarkers at the time of the study. One cohort (i.e., EPAD+) included two subcohorts (i.e., EMIF-Twins and EMIF-90+). Therefore, a total of eight cohorts were included in the meta-analysis: the Amsterdam Dementia Cohort (ADC),[30] Doetinchem Cohort Study (DCS),[31] EMIF-Twins,[32] EMIF-90+,[33] Longitudinal Aging Study Amsterdam (LASA),[34] Leiden Longevity Study (LLS),[35] Rotterdam Study,[36] and the SMART-MR Study.[37,38] The ADC came from a memory clinic, but only participants with subjective cognitive decline were included in the current study. The SMART-MR Study originated from a hospital setting where individuals all have a history of vascular disease. The other six cohorts were population-based studies. Only a small subsample from each cohort had plasma markers determined (total N = 7210). More information per cohort regarding participant selection for plasma assessment can be found in Supplementary Info 1.

Plasma Markers

The plasma markers (Aβ40, Aβ42, p-tau181, NfL, and GFAP) were measured using novel immunoassays in all cohorts except for EMIF-Twins and the Rotterdam Study. In brief, participants underwent venipuncture under non-fasting or fasting conditions (depending on the cohort) for EDTA-plasma sample assessment after storage. The Neurology 4-Plex E kit (Quanterix) was used for $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$, NfL, and GFAP.[39] P-tau181 was assessed using the p-tau181 Advantage V2 kit (Quanterix). Assays were run on-board of the Simoa HDx analyzer following manufacturer's instructions, using automated on-board sample dilution. Neurology 4-Plex kits were run in monoplo, and the p-tau181 kits were run in duplicates.

For EMIF-Twins, Aβ40 and Aβ42 were measured with in-house developed immunoassays ("Amyblood"; prototype of the Neurology 4-Plex E kit),[40] p-tau181 with a prototype immunoassay employing AT270 (Thermo Fisher Specific) and LRL (Eli Lilly and Company) antibodies and GFAP was assessed

with the commercially-available Simoa GFAP Discovery kit (Quanterix), using the Simoa HD-x analyzer, as described elsewhere.[32] NfL was not assessed in EMIF-Twins.

For the Rotterdam Study, the Simoa Neurology 3-Plex A assay was used to assess A$\beta_{x\text{-}40}$ and A$\beta_{x\text{-}42}$[41] and the Simoa NF-light advantage kit[42,43] to assess NfL on the Simoa HD-1 analyzer platform. P-tau181 and GFAP were not assessed in the Rotterdam Study.

All plasma measurements were performed at Amsterdam UMC, except for the Rotterdam Study. AD plasma biomarker assessment for ADC, DCS, LASA, LLS, and SMART-MR were all performed using the same kit lot number. EMIF-90+ was assessed with the same assays, but using different kit lot numbers. Further information regarding plasma storage and collection per cohort can be found in Supplementary Info 1.

Depressive Symptoms

Depressive symptoms were collected from validated questionnaires and included continuous sum scores. Depressive symptoms were collected at the same time-point as plasma measurements for all cohorts. For three cohorts (i.e., ADC, EMIF-90+, EMIF-Twins), the Geriatric Depression Scale-15[44] (GDS-15) was used. The total sum score on the GDS-15 is 15, with a higher score representing more depressive symptoms. LASA, LLS, and the Rotterdam Study used the Center for Epidemiologic Studies Depression Scale (CES-D).[45] The CES-D has a sum score up to 60 based on 20 items with a possible score of 0−3 per item. The SMART-MR study used the Patient Health Questionnaire-9 (PHQ-9).[46] The PHQ-9 has a total score of 27, based on nine items with scores ranging from 0−3 per item. The DCS used the Mental Health Inventory questionnaire (MHI-5).[47] The total score on the MHI-5 is up to 100, transformed based on a five-item questionnaire with a five-point scale regarding the frequency of positive and negative feelings. As higher scores on the MHI-5 reflect lower depressive symptoms, this questionnaire was reverse-coded. As questionnaires differed across cohorts, sum scores were standardized into z-scores. Additionally, we dichotomized these sum scores based on published cut-offs reflecting clinically relevant depressive symptoms. The cut-off for the GDS-15 was six or higher in the short form.[44,48] For the CES-D, a cut-off of 16 or higher was used.[49] For the PHQ-9, a cut-off of six or higher is used.[50] Last, for the MHI-5, we used a cut-off of 35 or lower.[51]

Covariates

Age and sex were assessed via self-report. Education was assessed categorically into less than high school education, at least some high school education, or college/university degree based on the Dutch education system. *APOE* ε4 allele (rs429358 C allele) presence was assessed via blood sample according to methods described previously[32,43,52–56] and defined dichotomously as the presence of at least one ε4 allele or not.

Statistical Analysis

For the first stage, standardized analyses were performed using R version 4.0.3[57] by E.T. locally per cohort. Multiple imputation of 10 imputed datasets was performed separately in each cohort with missing data using the *mice* package in R to address missing data. Both outcomes and predictors were imputed if needed,[58] using covariate information (i.e., age, sex, education, and APOE ε4 allele) as predictors in the imputation (see Table 1 for missing data per cohort). The same variables for imputation were used in each cohort. Linear regressions were performed to estimate the association between the plasma markers (determinant) and depressive symptoms (outcome). Logistic regressions were performed for the dichotomous outcome of high vs. low depressive symptomology. As assumptions were not met for linear regression based on non-normality, rank inverse normal transformation was done on the depressive symptom data.[59] Thereafter, models met all assumptions. Models were adjusted for age, sex, education, and presence of APOE ε4 allele. Sensitivity analyses were performed stratifying by sex and APOE ε4 allele status, and when excluding missing data (i.e., a complete case analysis). Further, analyses were performed assessing the interaction between sex and plasma marker and APOE ε4 allele status and plasma marker. Another sensitivity analysis was done on the models of Aβ42/40 by adding 1/Aβ40 and Aβ42 as main effects, as suggested by previous work on using a ratio in regression analyses.[60] Last, we also assessed as sensitivity analyses Aβ40 and Aβ42 as separate determinants for Aβ pathology.

TABLE 1. Cohort Demographic Characteristics

Cohorts	N	Setting	Age M (SD) (Range)	Sex N (%) Female	Education N (%) High	APOE ε4 Allelele N (%)
ADC	307	Memory clinic, subjective cognitive decline	60 (9) (38–82)	130 (42%)	174 (57%)	123 (40%)
DCS	365	General population	68 (3) (64–75)	177 (48%)	85 (23%)	108 (30%)
EMIF-90+	129	General population	92 (3) (85–102)	74 (57%)	23 (18%)	29 (22%)
EMIF-Twins	220	General population	71 (8) (60–94)	129 (59%)	22 (10%)	74 (34%)
LASA	370	General population	69 (7) (61–90)	203 (55%)	26 (7%)	161 (44%)
LLS	370	General population	67 (5) (55–85)	189 (51%)	121 (33%)	105 (28%)
Rotterdam study	4855	General population	72 (8) (58–99)	2783 (57%)	675 (14%)	1327 (27%)
SMART-MR	594	Patients with vascular disease, hospital-based	64 (8) (50–83)	101 (17%)	146 (25%)	184 (31%)
Total	7210					

Note: Imputed data is shown for cohorts with missing data.
For ADC, n = 1 missing for education and n = 15 missing for APOE ε4 allele genotype.
For DCS, n = 8 missing for APOE ε4 genotype.
For EMIF-90+, n = 26 missing on APOE ε4 allele genotype.
For EMIF-Twins, n = 4 missing on age, n = 3 missing on sex, n = 3 missing on education, and n = 6 missing on APOE ε4 allele genotype.
For LLS, n = 4 missing on education, n = 5 missing on APOE ε4 allele.
For Rotterdam Study, n = 2 missing on age, n = 70 missing on education, n = 242 missing on APOE ε4 allele genotype.
For SMART-MR, n = 5 on education and n = 27 missing for APOE ε4 genotype.

For stage two, effect estimates for each analysis were pooled using random-effects meta-analyses using R version 4.0.3[57] and *meta* and *metafor* packages.[61,62] A random-effects meta-analysis was chosen over a fixed-effects meta-analysis as a random-effects meta-analysis relatively weights the studies more equally when there is heterogeneity between studies.[63] Between-cohort heterogeneity was assessed via Cochran's Q. We also performed meta-regressions using the Omnibus test for moderators based on the mean age of the studies and the proportion of individuals with an APOE ε4 allele to see if these factors influenced meta-analysis results. As two cohorts used a different plasma assay (i.e., EMIF-Twins and the Rotterdam Study), we also performed sensitivity meta-analyses removing these two cohorts to see if that impacted the meta-analyses.

Statistical significance was set to p <0.01 for Bonferroni correction as we assessed four plasma markers: Aβ42/40, p-tau181, NfL, and GFAP.

RESULTS

Cohort Characteristics

Table 1 shows the demographic characteristics of each of the eight cohorts. Table 2 presents the distributions of the plasma biomarkers and depressive symptoms per cohort. In total, 7210 individuals were included in the meta-analysis. The total mean age was 71, and mean age per cohort ranged from 60 to 92 years. Percentage women per cohort ranged from 17% to 59%. Median values of the plasma biomarkers are provided in Table 2; prevalence of high depressive symptomology based on clinical cut-offs ranged from 1% to 22% per cohort.

Correlation matrices per cohort for age, depressive symptoms, and AD biomarker levels are shown in Supplementary Figure 1. A meta-analysis on the correlations between the plasma markers and age showed a positive correlation between p-tau181, NfL, and GFAP, and a negative correlation between Aβ42/40 and age (Supplementary Fig. 2). Men had lower levels of Aβ42/40 and GFAP (Supplementary Fig. 3). There was no difference in p-tau181 and NfL levels between men and women. APOE ε4 allele carriers had lower levels of Aβ42/40 and higher levels of GFAP (Supplementary Fig. 4), but no difference in levels of p-tau181 and NfL.

Meta-Analysis Findings

There was no evidence for an association between any of the AD plasma markers and depressive symptoms in the random-effects meta-analysis on the linear regressions (unstandardized regression coefficients B (95% CI), Aβ42/40: -0.01 (-0.04; 0.02), Z = -0.83,

TABLE 2. Descriptives of Plasma Biomarker and Depressive Symptoms Per Cohort

Cohorts	Aβ40 (pg/mL)	Aβ42 (pg/mL)	Aβ42/40 (pg/mL)	Ptau-181 (pg/mL)	NfL (pg/mL)	GFAP (pg/mL)	Depressive Symptoms N (%) High
ADC[a]	119 (107−135)	6.9 (6.1−7.6)	0.06 (0.05−0.06)	1.36 (1.06−1.99)	11.1 (8.5−15.4)	67 (48−98)	45 (15%)
DCS	119 (100−137)	6.7 (5.6−7.8)	0.06 (0.05−0.07)	1.51 (1.15−1.93)	15.6 (12.6−19.6)	106 (84−144)	78 (21%)
EMIF-90+[a]	110 (100−129)	7.7 (6.6−9.0)	0.07 (0.06−0.08)	3.02 (2.13−4.40)	44.4 (32.2−56.1)	186 (147−267)	10 (8%)
EMIF-Twins[a]	138 (124−154)	32.6 (28.4−37.8)	0.24 (0.21−0.26)	5.93 (4.97−7.49)	NA	134 (105−179)	3 (1%)
LASA	122 (108−138)	6.9 (6.1−8.0)	0.06 (0.05−0.06)	1.58 (1.24−2.11)	14.9 (11.7−20.1)	94 (73−131)	24 (6%)
LLS	126 (114−140)	7.3 (6.3−8.3)	0.06 (0.05−0.06)	1.43 (1.17−1.81)	15.4 (12.3−19.1)	99 (76−129)	81 (22%)
Rotterdam Study[a]	259 (229−293)	10.3 (8.9−12.1)	0.04 (0.04−0.05)	NA	13.3 (10.0−18.3)	NA	543 (11%)
SMART-MR	113 (99−130)	6.8 (5.8−7.7)	0.06 (0.05−0.07)	1.37 (1.05−1.84)	13.8 (10.1−19.8)	86 (61−115)	100 (17%)

Note: Median and interquartile range. Imputed data is shown for cohorts with missing data.
For ADC, n = 1 missing on both Abeta1-40, 1-42, GFAP, and NFL. N = 2 missing for Ptau-181 and n = 21 missing for depressive symptoms.
For DCS, n = 1 missing for depressive symptoms.
For EMIF-90+, n = 20 missing on all plasma marker data.
For EMIF-Twins, n = 14 missing on Abeta1-40, n = 33 missing on Abeta1-42, n = 26 missing on Ptau-181, n = 14 missing for GFAP, and n = 1 missing on depressive symptoms. NFL was not assessed.
For LASA, n = 1 missing on depressive symptoms.
For LLS, n = 2 missing on depressive symptoms.
For Rotterdam Study, n = 99 missing on depressive symptoms.
For SMART-MR, n = 5 missing for depressive symptoms. Aβ = amyloid-beta; Ptau = phosphorylated tau; GFAP = glial fibrillary acidic protein; NfL = neurofilament light.
[a] EMIF-Twins and the Rotterdam study use a different plasma assay. ADC and EMIF-90+ have been assessed at prior time points with a different batch.

p = 0.41; p-tau181: -0.03 (-0.06; 0.01), Z = -1.31, p = 0.19; NfL: 0.03 (-0.01; 0.08), Z = 1.34, p = 0.18; GFAP: 0.04 (-0.02; 0.10), Z = 1.41, p = 0.16; Fig. 1).

Due to a low number of individuals with high depressive symptomology (n = 3), logistic regression could not be performed in the EMIF-Twins study and therefore not included in the meta-analyses. Random-effects meta-analyses on logistic regressions also revealed no association with any plasma biomarker and high depressive symptomology (OR [95% CI], Aβ42/40: 1.00 [0.88; 1.14], Z = 0.03, p = 0.98; p-tau181: 1.01 [0.85; 1.20], Z = 0.09, p = 0.93; NfL: 1.12 [0.96; 1.31], Z = 1.39, p = 0.17; GFAP: 1.05 [0.92; 1.20], Z = 0.70, p = 0.48; Supplementary Fig. 5). Per cohort, results were similar to the linear regressions.

Subsequently, we performed a number of sensitivity analyses. When assessing women and men separately in linear regressions, higher levels of NfL were associated with higher depressive symptoms in women in the meta-analysis (B [95% CI]: 0.07 [0.03; 0.10], Z = 3.40, p <0.001, but not men (B [95% CI] : 0.01 [-0.04; 0.05], Z = 0.25, p = 0.80). However, there was no significant interaction with sex when adding an interaction term between sex and NfL to the linear regressions (B [95% CI]: 0.00 [-0.05; 0.05], Z = 0.06, p = 0.95, Fig. 2). There were no other sex differences in the other plasma markers with depressive symptoms (see Supplementary Table 1 for per cohort data).

When stratifying by APOE ε4 allele presence in the linear regressions, higher levels of NfL were associated with higher depressive symptoms in individuals with an APOE ε4 allele in the stratified meta-analyses (B [95% CI]: 0.11 [0.05; 0.17], Z = 3.75, p <0.001), while effects in APOE ε4 non-carriers were much smaller (B [95% CI]: 0.01 [-0.06; 0.07], Z = 0.19, p = 0.12). When adding an interaction term in the linear regressions of NfL and APOE, there was a significant interaction (B [95% CI]: 0.08 [0.02; 0.13], Z = 2.61, p < 0.01, Fig. 2). No other subgroup differences were found in other AD plasma markers for APOE ε4 carrier status (see Supplementary Table 1 for per cohort data).

Complete case analysis is shown in Supplementary Table 2. Main findings remained largely similar. When adding the main effects of Aβ42 and 1/Aβ40 to the Aβ42/40 ratio model, results for the linear regressions remained insignificant (B [95% CI]: -0.05 [-0.09; -0.01], Z = -2.53, p >0.01, Supplementary Fig. 6). When assessing Aβ40 and Aβ42 in separate linear regressions, both biomarkers showed higher levels associated with increased depressive symptoms (B [95% CI]: 0.07 [0.02; 0.12], Z = 2.79, p <0.01; B [95% CI]: 0.04 [0.02; 0.06], Z = 3.72, p <0.01, respectively,

Supplementary Fig. 7). When removing EMIF-Twins and the Rotterdam Study from our meta-analyses, most results remained similar. However, Aβ40 (B [95% CI]: 0.07 [-0.01; 0.15], Z = 1.73, p = 0.08) and Aβ42 (B [95% CI]: 0.05 [0.01; 0.10], Z = 2.41, p = 0.02) were no longer associated with depressive symptoms, and the interaction between NfL and APOE ε4 became marginally significant after multiple comparison adjustment (B [95% CI]: 0.10 [0.01; 0.19], Z = 2.27, p = 0.02).

Meta-regressions on mean age per study showed that age influenced the results of the meta-analysis on levels of NfL and depressive symptoms (*QM* = 10.78, df = 1, p = 0.001, Supplementary Fig. 8). For each increase of mean age per year per study, there was an increase of 0.01 in the z-score levels of NfL and depressive symptoms. For the meta-regression on proportion of APOE ε4 carriers per study, there was no evidence of an influence of levels of AD biomarkers and depressive symptoms.

DISCUSSION

In this meta-analysis on eight Dutch cohorts, where depressive symptoms are not severe or highly prevalent, we found no association between Aβ42/40, p-tau181, NfL, or GFAP and depressive symptoms. In the subgroup analyses, we found higher levels of NfL associated with depressive symptoms in individuals with an APOE ε4 allele, suggesting that in those individuals with a genetic risk for AD, neurodegenerative changes may underlie the occurrence of depressive symptoms.

We did not find an association between Aβ42/40 and depressive symptoms, which is not in line with a previous meta-analysis that found a relationship with lower levels of Aβ42/40 in those with depression compared to healthy controls.[21] However, all of those studies focused on a clinical population with depression, as well as included studies assessing serum Aβ, which has been shown to be less stable under storage conditions, compared to plasma Aβ.[64] Further, one recent study found a difference between Aβ42/40 between those with clinical depression compared to controls, but there was no cross-sectional association between depressive symptom severity and Aβ levels.[28] Therefore, subclinical levels of depressive symptoms may not be associated with accumulating Aβ levels. Additionally, our sensitivity analyses revealed an association with Aβ40 and Aβ42 separately with depressive symptoms. Since Aβ40 is more associated with arterial aging, cardiovascular disease, and platelet activation,[65,66] there is a possibility that our findings with the individual Aβ isoforms represent more of a vascular role rather than solely driven by AD pathophysiology. As our findings on Aβ42 were in the opposite direction than to be expected (i.e., higher levels associated with more depressive symptoms, whereas lower Aβ42 levels in plasma are associated with AD), our findings regarding the individual Aβ peptides should be interpreted with caution. Regarding tau pathology, a systematic review and meta-analysis on tau pathology and depression also did not find a relationship.[67] Our null finding in GFAP is not in line with previous literature that found an association with major depressive disorder in serum GFAP[26] and in CSF.[68] To our knowledge, no studies yet have been performed assessing GFAP with depressive symptoms. Similar to Aβ, there is a possibility that GFAP levels may be altered only when clinical depression is present.

Both depression and dementia are heterogeneous conditions, adding to the complexity of understanding their relationship. Depression has a wide variety of symptoms that may exist in subtypes,[69] and unfortunately in the present study we could not assess clusters of depressive symptoms due to differing questionnaires per study. There is a possibility that only a certain subtype of late-life depression is associated with an increased risk of dementia, such as through inflammatory or metabolic pathways.[70] Future studies should assess if a specific subgroup of late-life depression, focusing on both its pathophysiological and symptom-level characteristics, explains the link between depressive symptoms and dementia.

There is also a possibility that late-life depression may be driven by AD pathophysiology after cognitive symptoms begin, during the prodromal stage.[71] As most of the included cohorts were individuals without cognitive impairment (i.e., except for the ADC of individuals with subjective cognitive decline), there is a possibility that we did not find an association between AD pathophysiology and depressive symptoms as it may be too early in the disease process (i.e., during the preclinical stage, where amyloid accumulation is present without cognitive impairment).[72] AD pathophysiology may drive both cognitive and

FIGURE 1. Meta-analysis on linear regressions of AD plasma markers and depressive symptoms. ***Note:*** **Forest plots of the meta-analysis between the linear regressions on the plasma markers and depressive symptoms. Positive associations represent higher abnormal levels of each plasma marker with higher depressive symptoms. A null effect is represented by the dotted line, and the study weight is represented by the size of the squares. Coefficients are the unstandardized regression coefficients of each plasma marker per study.**

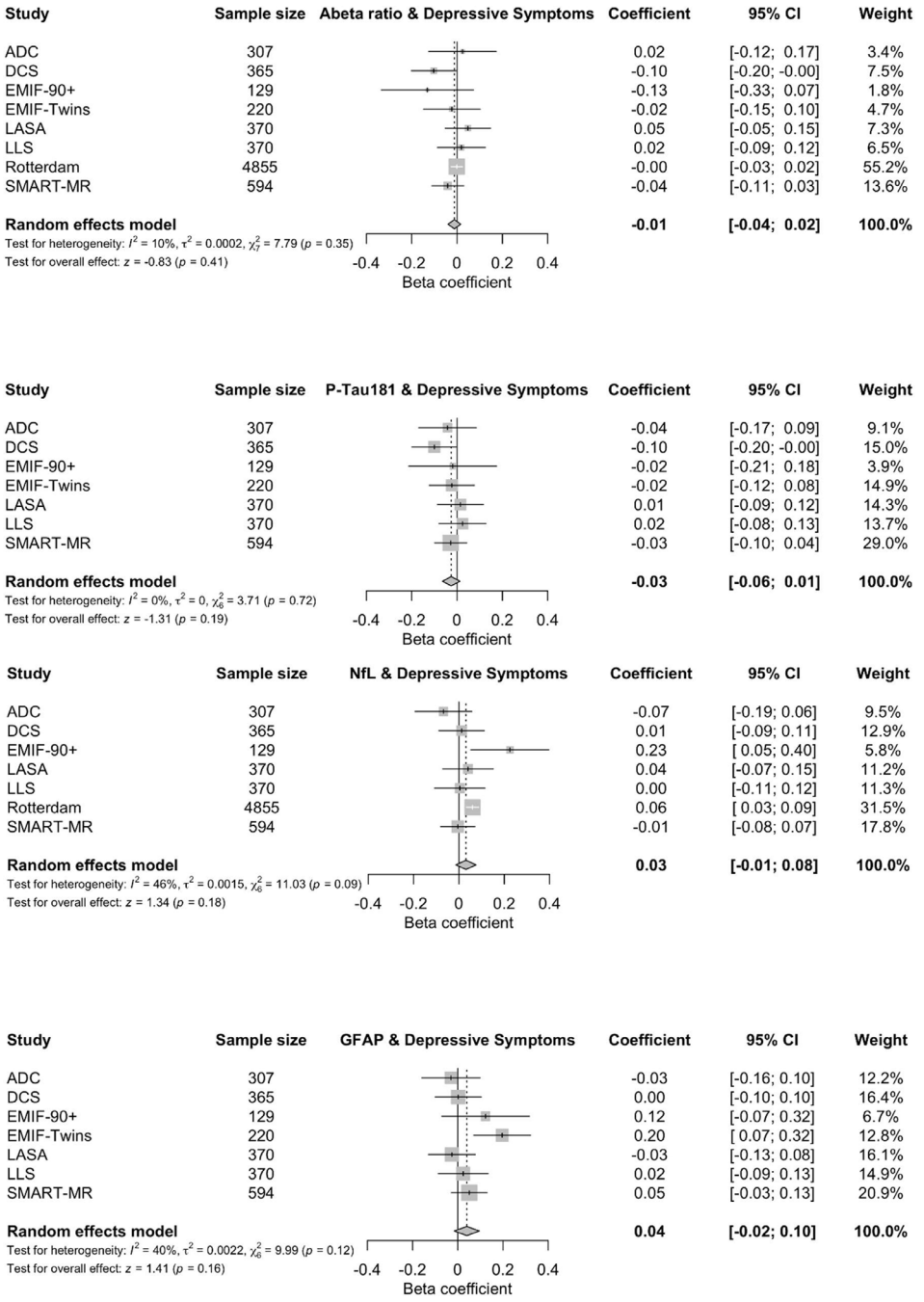
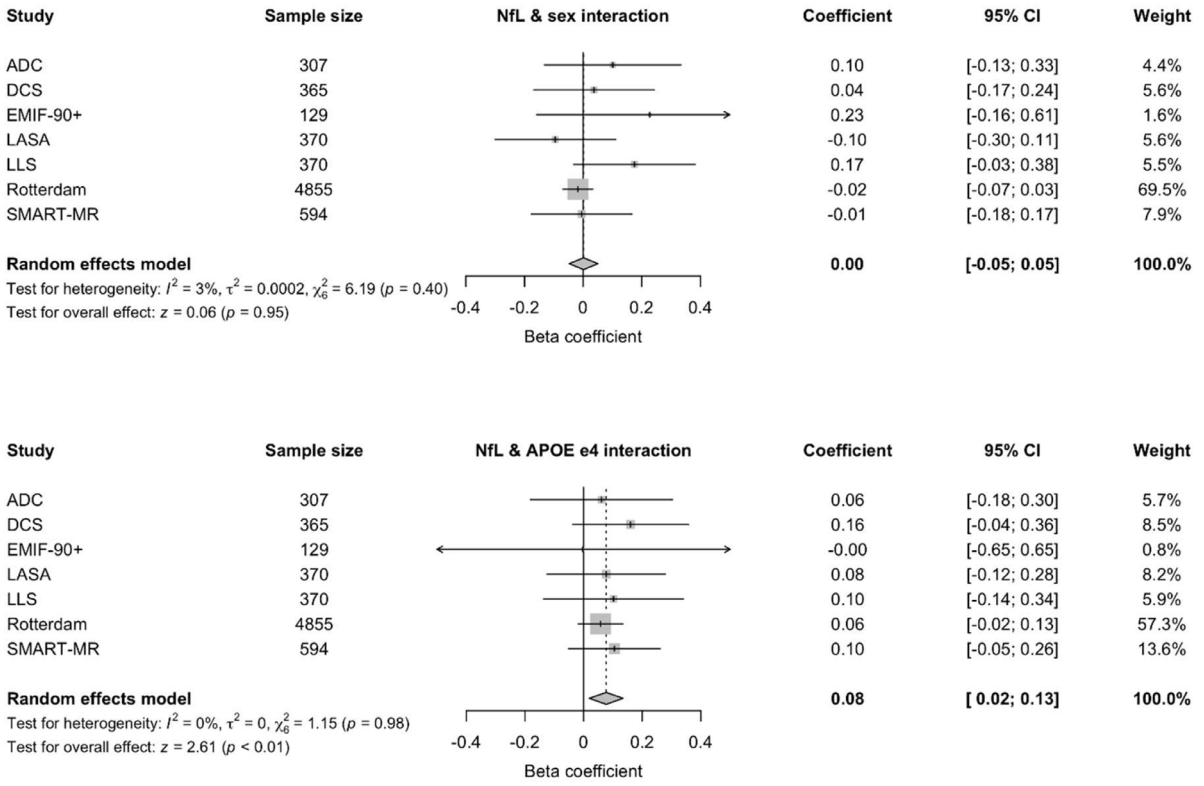


FIGURE 2. Meta-analyses on the interaction of NfL with sex and APOE ε4 carrier status. ***Note:*** **Forest plots of the meta-analysis between linear regressions on the interaction between NfL and sex or APOE ε4 allele and depressive symptoms. A positive interaction would signify higher levels of NfL associated with depressive symptoms in women or in APOE ε4 carriers. A null effect is represented by the dotted line, and the study weight is represented by the size of the squares. Coefficients are unstandardized regression coefficients of the interaction term between NfL and sex.**



psychological symptoms further into the disease trajectory after chronic accumulation. Previous literature has also suggested depression as being part of the prodromal stage of dementia.[12,73–75] Late-life depression could therefore be a reaction to AD pathology and perceived cognitive decline rather than being a risk factor.

Our results suggest a small association between NfL and depressive symptoms in individuals with an APOE ε4 allele. Possibly in individuals with high genetic risk for AD, increased axonal damage may underlie the occurrence of depressive symptoms, while in APOE ε4 noncarriers, depressive symptoms may have another origin. This may be explained by increased rates of neurodegeneration seen in those with an APOE ε4 allele.[76] Further, the presence of an APOE ε4 allele has been associated with late-life depression.[77,78] NfL has also been related to cerebral vascular damage,[79] perhaps explaining a vascular pathway to depressive symptoms. As literature on NfL in depression is limited,[80] particularly in population-based studies, more research is needed to validate these findings.

This meta-analysis has multiple strengths. By using a meta-analytical approach, we were able to gain power to assess the relationship between plasma AD biomarkers and depressive symptoms. Additionally, the ultrasensitive Simoa platform was used for biomarker assessments in most of the cohorts. Further, we harmonized methods across cohort studies, employed the same statistical procedure, and controlled for the same confounders.

Study also comes with some limitations. Depressive symptoms, as well as biomarker assessment, were collected at only one time-point. We also could not assess a temporal relationship between biomarker levels and depressive symptoms. Therefore, we could not infer causal directionality between neuropathology and depressive symptoms. Different depressive symptom questionnaires were also used amongst the cohorts, which could have increased heterogeneity and dampened replicability of our findings between the cohorts.[81] Due to data harmonization across cohorts, we also could not assess certain possible confounders such as cognitive functioning, kidney functioning, and antidepressant use. Further, while the majority of the cohorts benefited from the same assay procedure, two cohorts used a different assay to assess the plasma markers, which could have increased heterogeneity and decreased replicability as well. However, the lack of an association was mostly consistent across cohorts. Importantly, cohort participants were almost exclusively White individuals. As biomarker levels have shown to differ across ethnicities,[82,83] future studies should also assess the relationship between AD plasma biomarkers and depressive symptoms in other ethnicities.

Our study did not provide evidence for a direct link between plasma markers of the AD pathophysiological process and depressive symptoms. Subgroup analyses did suggest a more profound role of neurodegeneration and depressive symptomology in those with an APOE ε4 allele, but longitudinal studies are needed to elucidate the temporal role of depressive symptoms with neurodegeneration in genetically at-risk individuals.

THIS STUDY WAS CONDUCTED AS PART OF THE NETHERLANDS CONSORTIUM OF DEMENTIA COHORTS (NCDC)

NCDC receives funding in the Deltaplan Dementie from ZonMw (Project number 73305095005) and Alzheimer Nederland. The Leiden Longevity Study has received funding from the European Union's Seventh Framework Programme (FP7/2007-2011) under grant agreement number 259679, the Innovation-Oriented Research Program on Genomics (SenterNovem IGE05007), the Centre for Medical Systems Biology and the Netherlands Consortium for Healthy Ageing (grant 050-060-810), all in the framework of the Netherlands Genomics Initiative, Netherlands Organization for Scientific Research (NWO), BBMRI-NL, a Research Infrastructure financed by the Dutch government (NWO 184.021.007 and 184.033.111), and the Netherlands Consortium of Dementia Cohorts (NCDC), which is funded by Deltaplan Dementie from ZonMW Memorabel (project number 73305095005) and Alzheimer Nederland. This study was also supported by Alzheimer Nederland grant WE.03.2021-09 (PI Geerlings).

DISCLOSURES

No disclosures to report.

AUTHOR CONTRIBUTIONS

Study design was planned by ELT, IMWV., CT, MH, AALK, MB, DV, MAI, FJW, JEFM, LG, WMvdF, and MIG Data analyses were performed by ELT and MK Article was drafted by ELT The paper was edited and revised by all authors.

DATA STATEMENT

The research shown here has been presented by poster at the AAIC 2023 conference in Amsterdam, the Netherlands.

ACKNOWLEDGMENTS

We would like to gratefully acknowledge the participants from all eight cohort studies for their participation in this research. We thank the respondents, epidemiologists, and fieldworkers of the Municipal Health Service in Doetinchem for their contribution to the data collection for this study. We would like to gratefully acknowledge the SMART participants. We would like to acknowledge the following SMART research nurses, as well as R. van Petersen (data manager), B. G. F. Dinther (vascular manager), and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease-Study Group (UCC-SMART-Study Group: M.J. Cramer, H.M. Nathoe and M.G. van der Meer (co-PI), Department of Cardiology; G.J. de Borst and M. Teraa (co-PI),

Department of Vascular Surgery; M.L. Bots and M. van Smeden, Julius Center for Health Sciences and Primary Care; M.H. Emmelot-Vonk, Department of Geriatrics; P. A. de Jong, Department of Radiology; A.T. Lely, Department of Gynaecology and Obstetrics; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology & Hypertension; J.A.N. Dorresteijn (co-PI) and F.L.J. Visseren (PI), Department of Vascular Medicine, UMC Utrecht. Research of Alzheimer center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience.

Term Care. The Doetinchem Cohort Study (DCS) is supported by the Netherlands Ministry of Health, Welfare and Sport, Directorate Public Health and the National Institute for Public Health and the Environment. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The chair of Wiesje van der Flier is supported by the Pasman stichting. The SCIENCe project receives funding from Stichting Dioraphte. Research in LLS was supported by the ZonMw Project VOILA (457001001).

FINANCIAL SUPPORT

The Longitudinal Aging Study Amsterdam (LASA) Study is supported by a grant from the Netherlands Ministry of Health, Welfare and Sport, Directorate of Long-

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2024.03.004.

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