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10-Year trajectories of depressive symptoms and subsequent brain health in middle-aged adults

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ABSTRACT

Depressive symptoms differ in severity and stability over time. Trajectories depicting these changes, particularly those with high late-life depressive symptoms, have been associated with poor brain health at old age. To better understand these associations across the lifespan, we examined depressive symptoms trajectories in relation to brain health in middle age. We included 1676 participants from the ORACLE Study, all were expecting a child at baseline (mean age 32.8, 66.6% women). Depressive symptoms were assessed at baseline, 3 years and 10 years after baseline. Brain health (global brain volume, subcortical structures volume, white matter lesions, cerebral microbleeds, cortical thickness, cortical surface area) was assessed 15 years after baseline. Using k-means clustering, four depressive symptoms trajectories were identified: low, low increasing, decreasing, and high increasing symptoms. The high increasing trajectory was associated with smaller brain volume compared to low symptoms, not surviving multiple testing correction. The low increasing trajectory was associated with more cortical thickness in a small region encompassing the right lateral occipital cortex compared to low symptoms. These findings show that longitudinal depressive symptoms trajectories are only minimally associated with brain health in middle age, suggesting that associations may only emerge later in life.

1. Introduction

Depressive symptoms have been associated with several indicators of poor brain health, such as smaller hippocampi, smaller subcortical structure volume, and more cortical thinning (Binnewies et al., 2021; Kempton et al., 2011; Schmaal et al., 2020). Particularly in the elderly (age above 60), a greater presence of markers of cerebrovascular disease (Kales et al., 2005) has been reported, presented as more cerebral microbleeds (Wang et al., 2018), white matter lesions (Herrmann et al., 2008), and lacunar infarcts (Valkanova and Ebmeier, 2013). Findings have however been somewhat inconsistent, with some studies not replicating associations of depressive symptoms with smaller total brain volume or subcortical structure volume (e.g. the hippocampus) (Eker and Gonul, 2010; Gudmundsson et al., 2013; Perlman et al., 2017; Schmaal et al., 2020).

One aspect that may contribute to inconsistent results is whether depressive symptoms were assessed only once or repeatedly over time, as the experience of depressive symptoms differs in severity and stability over time. These trajectories of depressive symptoms can vary between and within individuals (Andreescu et al., 2008; Musliner et al., 2016), and are associated with different outcomes (e.g. Kuo et al., 2011). Yet, research assessing the relation between depressive symptoms and the brain often measure depressive symptoms at only one time point. One exception identified depressive symptoms trajectories over 25 years in 774 participants and found associations with brain health (Demnitz et al., 2020). More specifically, when compared to a low/no-symptoms trajectory, they found that the trajectory characterized by an onset of high depressive symptoms around the age of 65 had lower white matter microstructural integrity 5 years later, an association that was not found for the trajectory with consistently high depressive symptoms over time.

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Yet, whether these associations also emerge earlier in life remains unclear.

In this prospective population-based study, we examined the association between trajectories of depressive symptoms and several neuroimaging markers of brain health in middle-aged adults. We included pregnant women and their partners, established trajectories of depressive symptoms over approximately 10 years using three time points, and assessed how these trajectories were linked to global neuroimaging markers (total gray matter, total white matter), markers of cerebrovascular disease, local neuroimaging markers (volume or subcortical structure), and local differences in cortical thickness and cortical surface area of the brain. We expected to identify four different trajectories, in accordance with earlier work from our research group (Zou et al., 2019). Further, we anticipated that the trajectory with continuously high depressive symptoms would be associated with worse brain health as compared to other trajectories. No a-priori hypothesis were specified for trajectories that change over time.

2. Methods

2.1. Participants

The study was conducted within the Origins of Alzheimer's Disease Across the Life course (ORACLE) Study (Lamballais et al., 2021), which is embedded in the Generation R Study (Kooijman et al., 2016), a population-based prospective cohort from fetal life onwards that included pregnant women and their partners with a delivery date between April 2002 and January 2006. Approximately 15 years after initial inclusion in the Generation R Study, participating mothers and their partners were invited to take part in the ORACLE Study, which focuses on the life-course study of brain health. Participants underwent brain magnetic resonance imaging (MRI), cognitive testing, gait assessment, and multiple questionnaires about their health (Lamballais et al., 2021).

Of those who agreed to participate in the ORACLE Study ($n = 2083$), we excluded participants who were missing two or more depressive symptoms measurements ($n = 251$), without a T1-weighted or T2*-weighted scan ($n = 88$), with major incidental findings on brain MRI (i.e. brain pathologies that can bias brain structure estimates, for instance meningioma >3 cm) ($n = 59$), or without T1-weighted or T2*-weighted scans of insufficient quality ($n = 9$). The final study sample included 1676 participants.

General design, research aims, and specific measurements of the Generation R Study and the ORACLE Study have been approved by the Medical Ethical Committee of the Erasmus Medical Center, in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from all participants.

2.2. Depressive symptoms

Depressive symptoms of mothers and their partners were assessed at three different time points: when participant where expecting a child (mid pregnancy), 3 years after childbirth, and 10 years after childbirth. Mean ages were 32.8 ($SD = 4.8$), 36.5 ($SD = 1.1$), and 42.6 ($SD = 4.6$) over the three time points. Depressive symptoms during the past week were measured with depressive symptoms subscale of the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983). This scale consists of six items, which were scored on a five-point Likert scale (0 = not at all; 1 = a little; 2 = quite a bit; 3 = quite a lot, 4 = continually). If at least five out of six items were endorsed, item scores were summed and divided by the total of endorsed items to compute a weighted depressive symptom score (range 0–4). A score equal to or higher than 0.80 (women) or 0.71 (men) indicates clinically relevant depression (De Beurs and Zitman, 2005). The depressive symptoms scale from BSI has adequate reliability and validity (De Beurs and Zitman, 2005).

2.3. Imaging methods

Neuroimaging was performed 15 years after childbirth when parents were 47.6 years ($SD = 4.7$) years old, using a 3 Tesla GE Discovery MR750w MRI (General Electric, Milwaukee, WI, USA) with an 8-channel head coil. The imaging protocol and scanning parameters has been described elsewhere (Lamballais et al., 2021). Here we focus on the T1-weighted and T2*-weighted sequences.

T1-weighted images were processed using FreeSurfer 6.0 (Fischl, 2012). Images were segmented into gray matter, white matter, and cerebrospinal fluid. Surface-based models were generated, and each vertex was assigned an anatomical label from a predefined atlas (Desikan et al., 2006). We used the measures for total intracranial volume, total gray matter volume, cerebral white matter volume, white matter lesion volume, and volumes of subcortical structures (amygdala, hippocampus, thalamus, caudate, putamen, globus pallidus, and nucleus accumbens). Volume of left and right subcortical structures were averaged, as we did not expect lateralized effects. As the distribution of white matter lesion volume was skewed, the variable was log-transformed. Local cortical thickness and local cortical surface area were derived from vertex-wise data that were co-registered to a standard stereotaxic space and smoothed with a full-width half max kernel of 10 mm. The T2*-weighted images were manually inspected by trained researchers to detect cerebral microbleeds, which present themselves as small hypointense foci with a maximum size up to 10 mm. The quality of FreeSurfer output and T2*weighted images were visually inspected using a protocol similar to previously reported methods (e.g. Steenkamp et al., 2022), and data of insufficient quality were excluded.

2.4. Other variables

Date of birth, sex, education level, national origin, and smoking were self-reported at baseline (Kooijman et al., 2016). Education was categorized according to the classification of Statistics Statistics Netherlands (2016), separating low education (up to 3 years or less at secondary education or completed pre-vocational education), middle (more than 3 years of secondary education or completed vocational education), and higher education (completed higher professional education or university). National origin was categorized according to the classification of Statistics Netherlands (2004), which distinguishes 'Western' (Dutch, Western American, and European) and 'non-Western' (Indonesian, Cape Verdean, Moroccan, Antillean, Surinamese, Turkish, African, non-Western Asian, non-Western African). For women, past smoking was self-reported at baseline, while for men past smoking was reported by their partner (Kooijman et al., 2016). Past smoking was classified as ever/current or never.

Depressive symptoms at the time of neuroimaging were assessed with the Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report questionnaire developed to measure past week depressive symptoms among the general population (Beekman et al., 1997; Radloff, 1977). A score equal to or higher than 16 indicates clinically relevant depression (Beekman et al., 1997).

2.5. Statistical analysis

Statistical analyses were performed using R version 3.6.3 (R Core Team, 2020). First, we performed a non-response analysis, comparing the included participants to those that were eligible for participation in the ORACLE Study.

Trajectories of depressive symptoms were identified using K-means clustering as provided by the KML package (Genolini and Falissard, 2011). K-means clustering is a hill-climbing algorithm that clusters participants into homogeneous trajectories without a-priori assumptions on the shape of the trajectories. The final trajectory model was selected based on favorable Calinski and Harabasz criteria (Caliński and Harabasz, 1974) and correspondence with previous literature on depressive

symptoms trajectories (Cents et al., 2013; Musliner et al., 2016; Zou et al., 2019).

We assessed the association between depressive symptoms trajectories and continuous outcomes (total gray matter volume, cerebral white matter volume, white matter lesion volume, subcortical structures volumes) using linear regression. Dichotomous outcomes (presence of microbleeds) were assessed using binary logistic regression. To control for multiple testing we applied the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995). Local vertex-wise differences in cortical thickness and surface area were assessed using the QDECR R package (Lamballais and Muetzel, 2021). The QDECR R package runs linear regressions at each cortical vertex with depressive symptoms trajectories and covariates as predictors. To account for multiple testing within the vertex-wise analyses, we applied a cluster-wise correction using Gaussian Monte Carlo simulations. The cluster-forming threshold was set to $p = .001$, which corresponds closely to a false positive rate of .05 (Greve and Fischl, 2018). To account for testing two hemispheres separately, the vertex-wise analyses were additionally Bonferroni corrected.

All continuous outcomes were standardized. We adjusted for confounding in two confounding models. In the first model, analyses were adjusted for age during MRI and sex. Only analyses assessing subcortical structure volumes were additionally adjusted for intracranial volume. In the second model, analyses were additionally adjusted for education level at baseline, national origin, and past/current smoking at baseline. Missing data on BSI and covariates were imputed using multiple imputation using chained equations (mice) (Van Buuren and Groothuis-Oudshoorn, 2011). We imputed 30 datasets (60 iterations). Imputations were run using information from the predictor, outcomes, and covariates. Pooled regression coefficients were obtained using Rubin's rules (Rubin, 1987). Beta coefficients from all linear regression models are interpreted as standardized adjusted mean differences (i.e., z-score differences adjusted for covariates) between the trajectory of interest and the reference trajectory.

Two post-hoc analyses were performed. First, we examined the cross-sectional association of depressive symptomatology at the neuroimaging visit with neuroimaging markers. Second, we assessed whether associations remained when only including women, since the baseline measurement of depressive symptoms took place during pregnancy, when symptoms may have a different etiology (Brummelte and Galea, 2010; Payne and Maguire, 2019). Group sizes were too small to also restrict analyses to only men.

3. Results

3.1. Study population

The study population consisted of 1676 participants (66.6% women) with an average age of 32.8 years ($SD = 4.8$) at baseline and 47.6 years ($SD = 4.7$) during neuroimaging. Most of the participants followed intermediate education ($n = 828$, 52.2%) and had a Western national origin ($n = 1{,}321$, 83.2%). The non-response analyses indicated differences between the included participants and the Generation R Study sample, with less favorable socioeconomic status and health for those not included in the study sample (Table S1).

3.2. Depressive symptoms trajectories

Following the Calinski and Harabasz criteria, the first-best fit to model depressive symptoms trajectories was a 2-trajectory model, clustering 91.3% of the participants into a trajectory with low symptoms, and 8.7% of the participants in a trajectory with higher symptoms over time. The second-best fit was a 4-trajectory model, clustering participants in (1) a low symptoms trajectory ($n = 1{,}190$, 71.0%; reference category), (2) a low increasing symptoms trajectory ($n = 318$, 19.0%), (3) a decreasing symptoms trajectory ($n = 128$, 7.6%), and (4) a high increasing symptoms trajectory ($n = 40$, 2.4%) (See Fig. 1 for the summary graph; see Fig. S1 for a spaghetti plot). We used the 4-trajectory trajectory model in our analyses as this partitioning paralleled earlier work from our group (Cents et al., 2013; Zou et al., 2019) and retained more individual variability, allowing us to study differences within people with depressive symptoms. Demographic characteristics for the trajectory groups are shown in Table 1.

3.3. The association between depressive symptoms trajectories and brain health

Depressive symptoms trajectories were not associated with total brain volume (Table 2), markers of cerebrovascular disease (Table 2) or volumes of subcortical structures (Table 3). The high increasing symptoms trajectory was associated with a smaller total gray matter volume compared to the low symptoms trajectory, but not after multiple testing correction and only in model 1 (adjusted standardized difference = −0.28, 95% CI [−0.53, −0.03], $p = .026$, *p-adjusted* = .360). Further, participants in the high increasing trajectory also had a smaller accumbens compared to the low symptoms trajectory, but this was again not significant after multiple testing correction and only shown in model 2 (adjusted standardized difference = −0.28, 95% CI [−0.55, −0.01], $p = .043$, *p-adjusted* = .448).

Vertex-wise differences in cortical thickness were found for the low increasing symptoms trajectory, showing more cortical thickening in a region encompassing the right lateral occipital cortex (adjusted mm difference = 0.06, 95% CI [0.03, 0.09], $p < .001$, model 1; 0.06, 95% CI [0.03, 0.09], $p < .001$, model 2), see also Fig. 2. No local differences in cortical surface area were found.

3.4. Post-hoc analyses

Depressive symptoms at the moment of neuroimaging was associated to gray matter volume, but only in model 1 (adjusted standardized difference = −0.07, 95% CI [−0.11, −0.03], $p < .001$, *p-adjusted* = .010), and no other associations were found (Tables S2–S3, Figs. S2–S3). Further, when analyses were repeated within a subgroup of only women, results remained largely similar to the main results (Tables S4–S5, Fig. S4).

4. Discussion

We identified four distinct symptoms trajectories, namely a (1) low, (2) low increasing, (3) high increasing, and (4) decreasing symptoms trajectory in a population-based study following up on pregnant women and their partners, in accordance with our initial hypothesis. We did not find evidence that depressive symptoms trajectories over 10 years associate with gray or white matter volume, white matter lesions, cerebral microbleeds, or subcortical structures at middle age. Participants in the low increasing symptoms trajectory showed more cortical thickness in a small region encompassing the lateral occipital cortex, but no associations with surface area were found. Findings were consistent when restricting analyses to women. Together, our findings suggest that longitudinal depressive symptoms trajectories are minimally associated with brain health in the middle-aged general population.

Although previous research has found associations between late-life depressive symptoms and brain volume or markers of cerebrovascular disease (Demnitz et al., 2020; Herrmann et al., 2008; Kales et al., 2005; Wang et al., 2018), we did not identify these associations in middle age. This is in line with the study from Demnitz et al. (2020), which found that consistently high depressive symptoms (i.e., covering both middle and late life) do not associate with brain markers in elderly, whereas late-life depressive symptoms (i.e., covering only late-life) do. Their findings suggest that the association between depressive symptoms and the brain is either driven by its cross-sectional nature or otherwise by the timing of assessing the association (i.e., late in life). In our study, we did

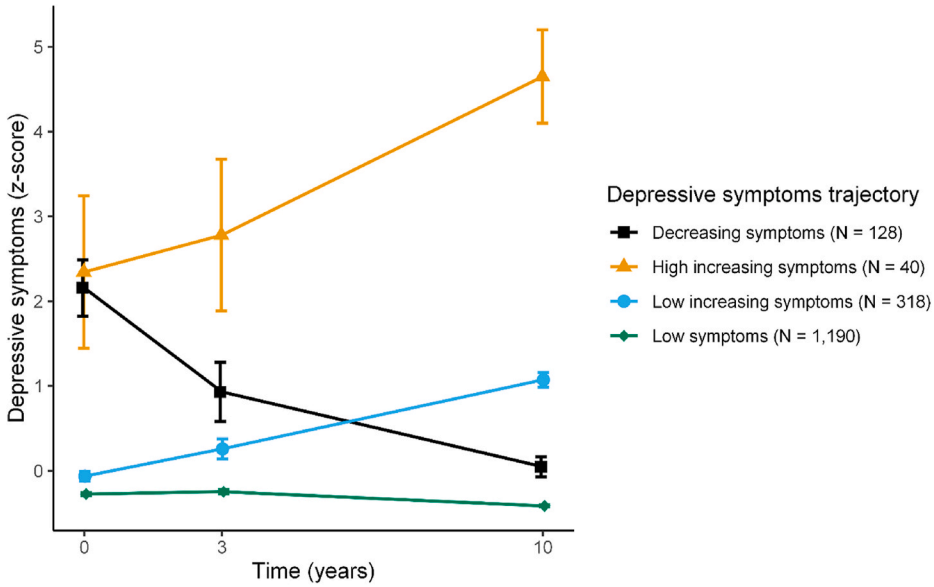


Fig. 1. Trajectories of depressive symptoms over 10 years.

Table 1
Sample characteristics per depressive symptoms trajectory.

	Low symptoms	Low increasing symptoms	Decreasing symptoms	High increasing symptoms
	M ± SD or N (%)	M ± SD or N (%)	M ± SD or N (%)	M ± SD or N (%)
N (% from total sample)	1190 (71.0)	318 (19.0)	128 (7.6)	40 (2.4)
Age, years	32.94 ± 4.48	32.75 ± 5.13	32.62 ± 5.97	28.20 ± 5.08
Sex, woman	759 (63.8)	231 (72.6)	94 (73.4)	33 (82.5)
National origin, Non-Western	155 (13.0)	53 (16.7)	43 (33.6)	13 (32.5)
Education level				
Low	108 (9.1)	30 (9.4)	25 (19.5)	10 (25.0)
Middle	573 (48.2)	167 (52.5)	68 (53.1)	20 (50.0)
High	452 (38)	99 (31.1)	27 (21.1)	8 (20.0)
Depressive symptoms				
BSI at baseline	0.03 ± 0.08	0.10 ± 0.14	0.75 ± 0.52	0.81 ± 0.79
BSI 3 years after baseline	0.03 ± 0.10	0.16 ± 0.24	0.32 ± 0.44	0.76 ± 0.63
BSI 10 years after baseline	0.03 ± 0.06	0.54 ± 0.26	0.19 ± 0.22	1.76 ± 0.55
CES-D 15 years after baseline	5.66 ± 5.54	10.23 ± 7.78	10.32 ± 6.82	18.79 ± 9.63
Clinically relevant symptoms				
Baseline	0 (0.0)	0 (0.0)	32 (25)	16 (40.0)
3 years after baseline	2 (0.2)	10 (3.1)	12 (9.4)	16 (40.0)
10 years after baseline	0 (0.0)	52 (16.4)	2 (1.6)	33 (82.5)
15 years after baseline	51 (4.3)	44 (13.8)	18 (14.1)	18 (45.0)

NB. All variables were measured during initial inclusion, except depressive symptoms. BSI = brief symptom inventory; CES-D = Center for Epidemiologic Studies Depression Scale.

Table 2
The association between trajectories of depressive symptoms trajectories and global brain volume and markers of cerebrovascular disease.

	Total gray matter	Cerebral white matter	White matter lesions	Cerebral microbleeds
	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Odds ratio (95% CI)
Model 1 (adjusted for age and sex)				
Low	Ref.	Ref.	Ref.	Ref.
Low increasing	−0.04 (−0.14, 0.05)	−0.09 (−0.19, 0.02)	−0.02 (−0.14, 0.09)	1.31 (0.89, 1.94)
Decreasing	−0.14 (−0.28, 0.00)	−0.12 (−0.27, 0.03)	0.05 (−0.12, 0.22)	0.84 (0.42, 1.65)
High increasing	−0.28* (−0.53, −0.03)	−0.22 (−0.49, 0.04)	−0.14 (−0.43, 0.16)	0.93 (0.28, 3.10)
Model 2. (adjusted for age, sex, education level, national origin, and smoking)				
Low	Ref.	Ref.	Ref.	Ref.
Low increasing	−0.02 (−0.11, 0.08)	−0.06 (−0.17, 0.04)	−0.03 (−0.14, 0.09)	1.32 (0.89, 1.96)
Decreasing	0.02 (−0.12, 0.16)	−0.01 (−0.16, 0.14)	0.04 (−0.14, 0.21)	0.90 (0.45, 1.78)
High increasing	−0.11 (−0.35, 0.13)	−0.12 (−0.38, 0.14)	−0.17 (−0.46, 0.13)	1.04 (0.31, 3.48)

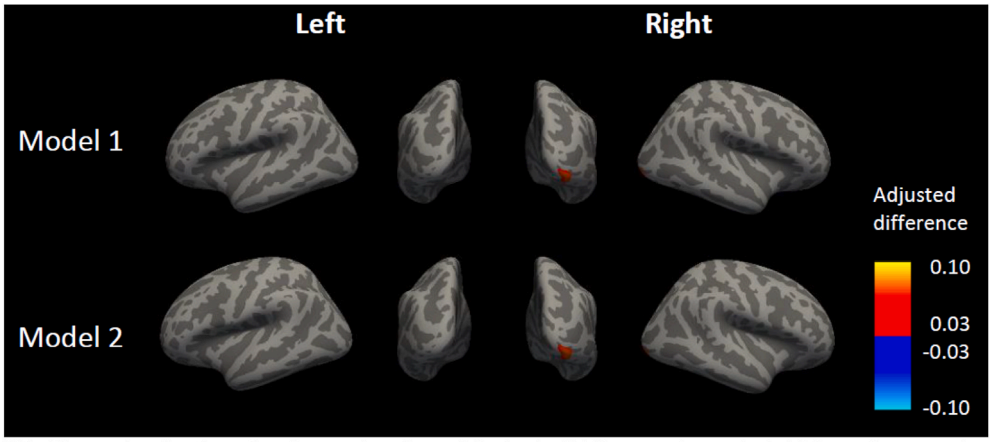
NB. Adjusted diff. = standardized adjusted mean differences (i.e., z-score) between the trajectory of interest and the reference trajectory, being the beta coefficients from linear regression models. *is significant at $p < .05$ before p-value correction.

not find evidence for a cross-sectional association between depressive symptoms and brain health, implying that the association between depressive symptoms and brain health is driven by when in life this association is assessed. Effects are most strong for depressive symptoms experienced later in life, when also brain health starts deteriorating (Ziegler et al., 2012). This could be explained by the association between late-life depressive symptoms and greater vascular risk (Demnitz et al., 2020). The vascular risk may in turn associates with a greater presence of markers of cerebrovascular disease (Aljondi et al., 2020; Ten Kate et al., 2018; Vernooij et al., 2008), which resembles poor brain health. Moreover, previous studies suggested that the causal relation may not only be from depressive symptoms to more markers of cerebrovascular disease, but also the other way around (van Sloten et al., 2015; Wang et al., 2018). This reversed association is posited by the vascular depression hypothesis, which implies that cerebrovascular disease may

Table 3
The association between trajectories of depressive symptoms and subcortical structures.

	Amygdala	Hippocampus	Thalamus	Caudate	Putamen	Pallidum	Accumbens
	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)	Adjusted diff. (95% CI)
Model 1 (adjusted for age, sex, and intracranial volume)							
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low increasing	−0.01 (−0.10, 0.08)	−0.04 (−0.14, 0.05)	0.06 (−0.02, 0.15)	−0.03 (−0.13, 0.08)	−0.04 (−0.14, 0.06)	−0.08 (−0.18, 0.02)	−0.10 (−0.20, 0.01)
Decreasing	0.04 (−0.10, 0.17)	−0.09 (−0.23, 0.05)	−0.08 (−0.20, 0.04)	−0.05 (−0.19, 0.10)	−0.05 (−0.20, 0.10)	−0.12 (−0.26, 0.03)	−0.14 (−0.29, 0.02)
High increasing	0.08 (−0.16, 0.31)	−0.13 (−0.37, 0.11)	0.04 (−0.17, 0.24)	0.09 (−0.17, 0.34)	0.24 (−0.01, 0.50)	0.12 (−0.13, 0.37)	−0.27 (−0.54, 0.00)
Model 2. (adjusted for age, sex, intracranial volume, education level, national origin, and smoking)							
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low increasing	−0.01 (−0.10, 0.08)	−0.04 (−0.14, 0.05)	0.07 (−0.01, 0.15)	−0.03 (−0.13, 0.07)	−0.04 (−0.14, 0.06)	−0.08 (−0.18, 0.01)	−0.10 (−0.20, 0.01)
Decreasing	0.03 (−0.11, 0.16)	−0.08 (−0.22, 0.07)	−0.06 (−0.18, 0.06)	−0.04 (−0.19, 0.11)	−0.07 (−0.22, 0.08)	−0.14 (−0.29, 0.01)	−0.15 (−0.31, 0.00)
High increasing	0.07 (−0.17, 0.30)	−0.13 (−0.37, 0.12)	0.05 (−0.16, 0.26)	0.10 (−0.16, 0.36)	0.23 (−0.03, 0.48)	0.10 (−0.15, 0.35)	−0.28* (−0.55, −0.01)

NB. Adjusted diff. = standardized adjusted mean differences (i.e., z-score) between the trajectory of interest and the reference trajectory, being the beta coefficients from linear regression models. *is significant at $p < .05$ before p-value correction.



NB. Figure showing lateral and posterior view of the brain. Differences in cortical thickness between the low symptoms and low increasing symptoms trajectories (lateral occipital cortex, size region model 1 = 359 mm^2; model 2 = 401 mm^2). Warmer colors represent cortical thickening, whereas cooler values represent cortical thinning. Results in model 1 are adjusted for age at MRI and sex. Results in model 2 are additionally corrected for educational level, national origin, and smoking.

Fig. 2. The association between trajectories of depressive symptoms and cortical thickness.

predispose, precipitate, or perpetuate some geriatric depressive syndromes (Taylor et al., 2013). Unfortunately, we did not have the opportunity to test reversed associations, as no baseline measures of cerebrovascular disease markers were available. Life-course models featuring repeated measures of neuroimaging and depressive symptoms are needed in the future to shed light on the causal relation between markers of cerebrovascular disease and late-life depressive symptoms across the life span.

Depressive symptoms trajectories and cross-sectional depressive symptoms were not associated to the volume of any subcortical structures after multiple testing correction, contrasting previous studies (Schmaal et al., 2020). However, the association between depressive symptoms and hippocampal volume has been suggested to be driven by early-onset and recurrent depression (Schmaal et al., 2020), a group that is potentially covered by our high increasing trajectory, although our results for this group did not reach significance. This may be due to power issues, as the sample size for the high increasing symptoms trajectory was small in our sample. Even so, results have been inconsistent across studies, with many studies not replicating the association between depressive symptoms and hippocampal volume (Eker and Gonul, 2010). It may be that associations with lower hippocampal volume are only found for patients with clinical major depressive disorders (e.g., Schmaal et al., 2020) as opposed to subclinical depressive symptoms. Also, depressive symptoms trajectories may not be associated with brain volume at middle age because effects might only emerge later in life when neuronal loss typically begins to accelerate (Ziegler et al., 2012).

Participants in the low increasing symptoms trajectory showed more cortical thickening in a small region comprising the lateral occipital cortex. This region is involved in the response to visual shape information and the processing of objects (Beauchamp, 2005), which may be increased in depression, especially towards negative stimuli (Gollan et al., 2008). However, in contrast with earlier literature on chronic major depressive disorder (Schmaal et al., 2020; Suh et al., 2019), we found *more* rather than less cortical thickness for the low increasing trajectory. This trajectory may particularly include participants with their first episode of depressive symptoms. We could speculate that when first experiencing depressive symptoms the body responds with proinflammatory cytokines (Dowlati et al., 2010). These cytokines activate astrocytes, which are associated to cellular hypertrophy (Liberto et al., 2004), potentially resulting in increased cortical thickness.

Indeed, more expression of genes marking astrocytes have been found to associate with increased cortical thickness (Shin et al., 2018). Also, first-episode depressive symptoms have repeatedly been associated with more cortical thickness (Qiu et al., 2014; Szymkowicz et al., 2016; van Eijndhoven et al., 2013). However, it has been suggested that once a person is experiencing depressive symptoms for a longer period of time, the neurotoxic effect of the extracellular glutamate may eventually lead to neuronal loss (Rajkowska and Miguel-Hidalgo, 2007), which could explain a reduction in thickness afterwards. We note that this is speculative since the region is small (surface of 420 mm^2) and could be explained by motion artefact or variance. Future studies should investigate this region further and should consider whether depressive symptoms are experienced for the first time, or rather are recurrent, as the episodic nature of depression may influence the direction of results.

In this population-based study, we used repeated measurements of depressive symptoms and have associated those to an extensive selection of neuroimaging measures, while adjusting for several confounders. Our work should however be interpreted in the light of the following limitations. Depressive symptoms trajectories were based on the depressive subscale from the BSI (Derogatis and Melisaratos, 1983). This scale consists of only six items, making it more prone to measurement error compared to more comprehensive diagnostic measures. Our findings may be complemented by studies using other instruments to measure depressive symptoms. Second, as the study sample is population-based and middle-aged, participants were relatively healthy. Only a small group of participants were in trajectories with more depressive symptoms and only a small group had poor brain health. Also, the use of a population-based simple limits the generalizability of findings to those with a clinical diagnosis of a depressive disorder. Third, use of antidepressants could confound or mediate our associations. We however could not check this confounding or mediation as we do not have this information available over the full time period. For reference, at baseline only 1.5% of the women reported usage of serotonin reuptake inhibitors or tricyclic antidepressants during pregnancy, no women reported the use of monoamine oxidase inhibitors. Fourth, baseline measurements were performed when participants were expecting a child. Although pregnancy in general is considered to be a positive life event, women also experience decreased physical health and more depressive symptoms during this period (Haas et al., 2005; Setse et al., 2009). Therefore, depressive symptoms may have been more pronounced during the baseline measurement. Relatedly, results may have been influenced by the specific etiological mechanisms behind prenatal depressive symptoms (Brummelte and Galea, 2010; Payne and Maguire, 2019). Future studies are needed to understand if depressive symptoms during pregnancy may have a differential impact on brain health than at other times in life. Fifth, selection bias is potentially induced as persons who expect a child may differ from those who do not become parents in their life. Finally, regardless of our large sample, we did not have the opportunity to study the association in men only, as the sample sizes for some trajectory groups would be very small. Future studies should be performed in large consortiums, enabling sex-specific analysis.

In conclusion, we found weak to no evidence for associations between depressive symptoms trajectories and brain volume, markers of cerebrovascular disease, and cortical surface area in middle-age. Participants with low increasing depressive symptoms over time did show more cortical thickness in a small region encompassing the lateral occipital cortex. Together, this suggests that depressive symptoms trajectories do not have a marked influence on brain health at middle age, although associations may emerge in old age.

NB. Figure showing lateral and posterior view of the brain. Differences in cortical thickness between the low symptoms and low increasing symptoms trajectories (lateral occipital cortex, size region model 1 = 359 mm^2; model 2 = 401 mm^2). Warmer colors represent cortical thickening, whereas cooler values represent cortical thinning. Results in model 1 are adjusted for age at MRI and sex. Results in model 2 are additionally corrected for educational level, national origin, and smoking.

Data availability

All relevant summary data supporting this study are available within the article and its supplementary information files. Due to ethical and legal restrictions, individual-level data of the Generation R Study cannot be made publicly available. These data are available upon request to the data manager of the Generation R Study (Claudia Kruithof; c.kruithof@erasmusmc.nl) and subject to local rules and regulations. This includes submitting a proposal to the management team, where upon approval, analysis needs to be done on a local server with protected access, complying with good data practice regulations.

Author contributions

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

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.12.018.

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