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# The relationship between depression and executive function and the impact of vascular disease burden in younger and older adults

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## Abstract

**Background:** depression is associated with worse executive function, but underlying mechanisms might differ by age.

**Aims:** to investigate whether vascular disease burden affects the association between depression and executive dysfunction differentially by age.

**Method:** among 83,613 participants of Lifelines (population-based cohort study), linear regression analyses were applied to examine the association between executive function (Ruff Figural Fluency test, dependent variable) and depression according to DSM-IV criteria (Mini International Neuropsychiatric Interview, independent variable).

**Results:** adjusted for demographic characteristics, major depressive disorder was associated with a lower level of executive function in both younger and older adults. Minor depressive disorder was only associated with worse executive function in younger adults. Adding vascular disease burden to the final model with major depressive disorder, reduced this strength of this association by 5.9% in younger and 5.0% in older adults.

**Conclusions:** major depression was associated with worse executive function across the lifespan, but minor depression only in younger adults. The impact of vascular burden on the association did not differ between younger and older adults. Therefore, vascular risk reduction is important in both age groups

**Keywords:** *depression, cognitive function, executive function, vascular disease, older people*

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## Introduction

Depression is associated with deficits in multiple cognitive domains (executive function, attention and memory) [1, 2] in younger [3] and older persons [4]. However, the underlying mechanisms may differ by age. For instance, cognitive reserve capacity is lower in older persons [5], resulting in a higher impact of a depressed mood state on cognitive function. In line with this idea, minor depression is associated with worse cognitive function in older adults [6, 7], but not in younger adults [8]. In addition, vascular risk

factors are assumed to contribute to cerebrovascular disease [9]. Cerebrovascular disease has been found to be associated with executive dysfunction [10] and depressive symptoms [11]. As cerebrovascular disease burden increases with age it may more likely underlie the association between depression and poor executive function in older than in younger adults. Remarkably, only a few small case-control studies have directly compared the association between depression and executive function between age groups and found no difference in the association between depression and executive function according to age group [12, 13].

Within a large population-based study, we investigated the relationship of major and minor depressions with executive function and determine whether the impact of vascular burden on this relation differs by age. We hypothesised that major depression is associated with worse executive function in all adults, but that minor depression only in older adults. In addition, we hypothesised that vascular burden explains the association between depression and executive function more in older than in younger adults.

## Method

Full methodology can be found in Supplementary data available in *Age and Ageing* online.

### Study design and sample

This study used the baseline-data of the Lifelines study with a total of 167,729 participants from the general population [14]. Participants <18 years, with a neurological disorder or Mini Mental State Examination (MMSE) <26 were excluded ( $n = 20,317$ ), resulting in a total of 147,412 eligible participants.

### Measures

*Depression:* was assessed according to the DSM-IV criteria for either a current major or minor depressive episode using the Mini International Neuropsychiatric Interview (MINI) [15].

*Executive function:* was assessed with the total number of unique designs on the Ruff Figural Fluency Test (RFFT) [16].

*Co-variables:* were gender, age, educational level, Framingham Risk Score (FRS) [17] and presence of vascular disease.

### Statistical analysis

First, baseline characteristics were compared between younger and older adults and between persons with minor, major or no depression. Next, we investigated whether the association of the RFFT score with depression was dependent on age using an interaction term of depression  $\times$  age. After this, multivariable linear regression models were used to investigate the association of minor and major depression with RFFT-scores in younger and older adults ( $\geq 60$  years; unadjusted, adjusted for demographics and adjusted for demographics and vascular burden).

## Results

### Baseline characteristics

Of 147,412 eligible persons, 83,613 had complete data (partly due to the fact that the RFFT was administered only every other week after 2012). Those with missing data had somewhat more often minor depression, but differences on other characteristics were very small (see Supplementary data, Table 1, available at *Age and Ageing* online). Older adults ( $n = 10,620$ ) had worse RFFT scores, were less often female, had a lower educational level, less often had major depression, had a worse FRS and a higher prevalence of vascular disease than younger adults ( $n = 72,993$ ; Table 1). See Supplementary data, Table 2, available at *Age and Ageing*

**Table 1.** Baseline characteristics of the total group and split at 60 years (younger and older adults)

	Total data ( $n = 83,613$ )	Younger adults ( $<60$ years; $n = 72,993$ )	Older adults ( $>60$ years; $n = 10,620$ )	Test statistic
RFFT-score				
Mean (SD)	81 (23)	84 (22)	63 (20)	$T(14,563,548) = 97,612^{***}$
Gender				
Female	49,177 (58.8%)	43,349 (59.4%)	5,828 (54.9%)	$\chi^2(1) = 77,860^{***}$
Age (years)				
Mean (SD)	44 (12)	41 (10)	66 (5)	
Educational level (ISCED)				
Primary or lower	1,971 (2.4%)	1,148 (1.6%)	823 (8.2%)	$\chi^2(5) = 4,798.439^{***}$
Lower secondary	11,154 (13.7%)	8,664 (12.1%)	2,490 (24.9%)	
Upper secondary	11,601 (14.1%)	9,142 (12.8%)	2,459 (24.6%)	
Post secondary	25,505 (31.2%)	23,816 (34.1%)	1,689 (16.9%)	
First tertiary	26,636 (32.6%)	24,423 (34.1%)	2,213 (22.1%)	
Second tertiary	4,872 (5.9%)	4,508 (6.3%)	319 (3.2%)	
Depression				
No	79,126 (94.6%)	69,017 (94.6%)	10,109 (95.2%)	$\chi^2(2) = 22,629^{***}$
Minor depression	2,599 (3.1%)	2,260 (3.1%)	339 (3.2%)	
Major depression	1,888 (2.3%)	1,716 (2.4%)	172 (1.6%)	
FRS				
Median (IQR)	1 (-1; 4)	1 (-1; 3)	3 (1; 5)	$U = 59,179^{***}$
Vascular disease				
No	79,512 (97.4%)	70,350 (98.5%)	9,162 (90.0%)	$\chi^2(1) = 2,601.054^{***}$
Yes	2,095 (2.6%)	1,072 (1.5%)	1,023 (10.0%)	

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  (Test statistic:  $t$ -test, chi-square, Mann-Whitney  $U$ ).

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online for the differences between persons with no, minor or major depression.

## Interaction age × depression

There was a significant interaction effect between minor depression × age on the RFFT ( $P = 0.003$ ), but not for major depression × age on the RFFT ( $P = 0.341$ ).

## Association between depressive disorder, executive function and vascular burden

In younger adults (<60 years) depressive disorder (minor and major) was significantly associated with worse RFFT-scores, adjusted for demographics and vascular burden. Adding vascular burden attenuated the regression coefficient with 5.9%. In older adults major depression was significantly associated with worse RFFT-scores adjusted for demographics and vascular burden. Adding vascular burden to the model attenuated the regression coefficient with 5.0%. Minor depression was not significantly associated with worse RFFT-scores, adjusted for demographics (Table 2).

## Discussion

### Summary of findings

This large population-based study confirmed previously established associations between major depressive disorder and worse executive function in younger and older adults. In contrast to our hypotheses, minor depressive disorder was only associated with worse executive function in younger adults and the impact of vascular burden on the association between major depression and executive function did not differ by age.

## Depression and executive function

The association between major depression and worse executive function in both age groups is consistent with literature [1, 2, 3]. This association might be due to both structural as well as functional abnormalities in the prefrontal cortex [2]. This study is the first large population-based study to find minor depression to be associated with worse executive function in (younger) adults (<60 years). Meta-analyses have found an association between severity of major depression and worse executive function [2], which might indicate that impairment of executive function is sensitive to the severity of depression symptoms. To the best of our knowledge, the only study who investigated this relationship in younger adults (aged 20–64 years). This study did not find an association between minor depression and impaired executive function [8]. The small sample size of the previous study (only 66 persons with minor depression), as well as the use of another neuropsychological test (Trail-Making-Test) may explain this difference. Our findings suggest that worse executive function is also present in younger adults with minor depression.

In this large population-based study, we found no association between minor depression and worse executive function in older adults. This is consistent with one study [4], but contrasts other studies [6, 7]. An explanation for this difference might be that we applied DSM-IV criteria to assess minor depressive disorder, whereas previous studies are based on depressive symptom severity scales like the Geriatric Depression Scale or Center for Epidemiological Studies Depression scale (CES-D) (e.g. [7]). Consistent with this explanation, the prevalence of minor depressive disorder was 3.2% in our study, which is below the pooled prevalence rate of 13.5% for clinically relevant depressive symptoms as identified by meta-analyses in community-based studies [18]. This is very relevant, as prevalence rates based on self-report depressive symptom questionnaires are easily inflated due to confounding by underlying somatic

**Table 2.** Impact of depression on (executive) cognitive performance in younger and older adults adjusted for demographic variables and vascular burden

	Unstandardised regression coefficient (95% CI) <sup>a</sup>	
	Younger adults (18–60 years; $n = 67,318$ ) <sup>b</sup>	Older adults (>60 years; $n = 9,402$ ) <sup>b</sup>
Minor depression		
Unadjusted	–6.880*** (–7.861/–5.889)	–4.508*** (–6.874/–2.142)
Adjusted for demographic variables	–3.999*** (–4.921/–3.077)	–1.701 (–3.862/0.461)
Adjusted for demographic variables and vascular burden	–3.857*** (–4.778/–2.935)	–1.377 (–3.536/0.782)
Change regression coefficient when adding vascular burden (%)	3.6%	19.0%
Major depression		
Unadjusted	–7.775*** (–8.914/–6.636)	–6.541*** (–9.865/–3.216)
Adjusted for demographic variables	–4.294*** (–5.365/–3.223)	–5.103** (–8.139/–2.068)
Adjusted for demographic variables and vascular burden	–4.040*** (–5.112/–2.968)	–4.846** (–7.876/–1.816)
Change regression coefficient when adding vascular burden (%)	5.9%	5.0%

<sup>a</sup>Linear regression with RFFT-score as the dependent variable, unadjusted, adjusted for demographic variables (age, gender and level of education) and fully adjusted (demographic and vascular burden (vascular burden includes FRS and vascular disease)).

<sup>b</sup>This is the  $n$  with data on all variables in the final model.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

illness [19] and cognitive disorders [20], which potentially influenced the results of the previous studies.

Taken together, our data suggest that minor depression according to DSM-IV criteria is associated with worse executive function in cognitively healthy younger adults, but not in cognitively healthy older adults.

### **Influence of vascular disease burden**

To the best of our knowledge, this is the first study that directly compared the impact of vascular burden on the association between depression and executive function in younger and older persons. Our results suggest that the impact of vascular burden is similar in younger and older adults. This is consistent with a previous study that found vascular risk factors to have a stable negative impact on executive function in younger and older adults [21]. Cerebrovascular damage has been associated with depression [11] as well as executive dysfunction [10] in older age. However, evidence of the detrimental effect of vascular risk factors in younger adults is increasing [21, 22]. Our study underlines this negative impact of vascular burden on executive function in younger and older adults. Therefore, vascular risk reduction is important in both age groups.

### **Strengths and limitations**

Despite the large sample size, wide age-range, formal psychiatric diagnostics and sensitive test of executive function, some limitations should be addressed. First Lifelines was a volunteer cohort, but broadly representative to the population of the north of the Netherlands. Nonetheless, participants were slightly higher educated and less often smoked [23]. Therefore, generalisation to lower educated persons might be limited. Second, our study is a cross-sectional study, so no conclusion can be drawn regarding the influence of time on our results. Longitudinal studies are warranted to investigate whether executive dysfunction persists after remission of depression in these age groups. Third, we measured executive function by one test. Although the RFFT is sensitive to subtle changes in cognitive performance in younger and older adults [24], the use multiple neuropsychological tests to assess (different domains of) executive function might increase the generalisability of our findings. Fourth, older persons with MMSE <26 were excluded from the present analyses because they were not administered the RFFT and the MINI; however, the MMSE was not administered to younger persons. Nonetheless, previous studies have shown that it is exceptional that younger persons in the general population will score <26 on the MMSE [25]. Therefore, it remains unclear to what extent the present findings are generalisable to older adults with lower MMSE scores. Fifth, we did not perform MRI as a more accurate assessment of cerebrovascular damage. Finally, this study design had a high number of missing data. However, participants with missing data (RFFT/MINI) showed minimal differences.

### **Clinical implications**

We found major depression to be associated with worse executive function in younger and older adults and minor depression only in younger adults. As executive dysfunction in depression has been associated with worse response to pharmacological treatment [26], different treatment strategies targeting executive dysfunction are warranted (such as problem solving therapy or new pharmaceuticals). Our study showed a similar impact of vascular burden on the association between depression and executive function in younger and older adults, underlining the importance of treating/preventing vascular disease also in younger adults. A future study should preferably be longitudinal, include MRI assessments and include a more extensive cognitive test battery in order to evaluate the temporal order of depression, the progression of cerebrovascular disease and the development of deficits in executive function or other cognitive domains.

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### **Key points**

- Major depression is associated with worse executive function across the lifespan.
- Minor depression is associated with worse executive function in younger adults but not in older age, which might be explained by the heterogeneous nature of minor depression in later life.
- The negative impact of vascular burden is similar across the lifespan.

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### **Supplementary data**

Supplementary data are available at *Age and Ageing* online.

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