Lower serum BDNF as a predictor of post-stroke cognitive impairment in acute ischemic stroke patients [version 1; peer review: awaiting peer review]

Ismail Setyopranoto1, Astuti Prodjohardjono1, Sri Sutarni1, Noor Alia Susianti2, Muhammad Hardhantyo3,4, Amelia Nur Vidyanti1

1Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
2Neurology Research Office, Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
3Center of Health Policy and Management, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
4Faculty of Health Science, Universitas Respati Yogyakarta, Yogyakarta, 55281, Indonesia

Abstract

Background: Reduced level of serum BDNF in acute stroke patients is associated with poor outcomes. We aimed to identify the role of serum BDNF level as a predictor for post-stroke cognitive impairment (PSCI).

Methods: This was a prospective study. We recruited acute ischemic stroke patients in Dr. Sardjito General Hospital Yogyakarta, Indonesia followed them up for 90 days (3 months). Serum BDNF was collected at day 5 and day 30 of stroke onset and measured by ELISA. Montreal Cognitive Assessment (MoCA) was used to measure the cognitive function at 90 days of follow up. ROC curve was conducted to measure the cut-off point of the BDNF level. Factors independently associated with PSCI were analyzed by using stepwise regression.

Results: Among 89 patients recruited, 60 patients (67.41%) developed PSCI. The mean age of PSCI and non-PSCI patients was 62.7 ± 9.5 and 57.5 ± 8.7, respectively (p = 0.01). Patients with dyslipidemia were less likely to develop PSCI (OR 0.19, 95%CI 0.06–0.56, p < 0.05). In addition, patients with day 5-serum BDNF level < 23.29 ng/mL were five times more likely to develop PSCI compared with their counterparts (OR 5.02, 95%CI 1.67–15.04, p < 0.05).

Conclusions: Among acute ischemic stroke patients, those with serum BDNF <23.29 ng/mL had a higher risk of developing PSCI, while those with dyslipidemia had a lower risk of PSCI. This study suggests that BDNF could be a predictor of PSCI, allowing for earlier detection and better preventive strategies.
Keywords
serum BDNF, predictor, post-stroke cognitive impairment, acute ischemic stroke
**Introduction**
Among the stroke survivors, post stroke cognitive impairment (PSCI) is one of the common complications after stroke. Approximately, 53.4% post stroke patients suffered from PSCI which ranged from mild to severe cognitive impairment.1 The cognitive impairment will lead to severe disability and increase the cost of health care after stroke attacks.2,3 Nowadays, the investigations of biomarkers are developed to predict the long-term outcome and cognitive impairments after stroke. There are several growth factors that can affect the prognosis of patients with ischemic stroke in the long term, for example VEGF (vascular endothelial growth factor), BDNF (brain-derived neurotrophic factor), G-CSF (granulocyte-colony stimulating factor), Ang1 (angiopoietin 1), and SDF-1α (stromal-derived factor-1α).4–6

The most prevalent neurotrophin, Brain-derived Neurotrophic Factor (BDNF), is involved in neuronal survival, synaptic plasticity, angiogenesis, as well as neurite outgrowth in peripheral and central nervous systems.7,8 Both intravenous and intraventricular BDNF infusions reduced infarct size and showed neuroprotective benefits in experimental stroke model studies. Furthermore, there is evidence that BDNF is linked to various neuropsychiatric diseases.9

Another experimental study showed that local administration of BDNF ameliorates the functional motor recovery in ischemic stroke models.10 In human study, reduced level of serum BDNF has been found in acute ischemic stroke patients and is associated with poor functional outcome as well as more dependency.6,11–13 BDNF could improve brain plasticity and neuronal repair after stroke by promoting angiogenesis dan neurogenesis.14 Previous studies conducted among patients free of stroke revealed that higher BDNF was associated with better visual memory and global cognitive function.15,16 However, none of those previous studies investigated about the role of BDNF as a biomarker for predicting the development of PSCI among acute ischemic stroke patients.

Assuming that the serum BDNF levels reflect brain levels, it seemed rational to think that measuring serum BDNF levels in the early stages of stroke would be effective for stroke outcome prediction. The present study aimed to identify the role of serum BDNF level in acute ischemic stroke patients in predicting PSCI. By understanding the important role of BDNF, the development of PSCI may be detected earlier thus early intervention can be applied leading to reduce the long-term disability, social, and economical burden caused by PSCI.

**Methods**

**Study design and participants**
This was a prospective study. The data was collected from June 2019 to May 2020. We recruited patients with acute ischemic stroke in Dr. Sardjito General Hospital Yogyakarta, Indonesia.

We included patients with: (1) first-ever stroke with the stroke onset within 5 days; and (2) aged >18-years old. We excluded those with: (1) recurrent stroke patients; (2) brain tumor, brain trauma, encephalitis, Parkinson’s disease, epilepsy, and dementia; and (3) depression or history of psychiatric diseases.

Demographic, clinical, and laboratory data included serum BDNF were collected at day-5 of the stroke onset during hospitalization. In total, 89 eligible patients were selected during the study period.

**Data collection**

**Outcome variable**
The outcome variable was PSCI developed 3 months after stroke onset. We assessed the cognitive function at day 5, 30, and 90 after stroke onset by using Montreal Cognitive Assessment-Indonesian version (MoCA-INA) which has been validated for Indonesian population.17 PSCI group was defined if the total score of MoCA-INA at 90 days (3 months) after stroke was < 26.18 Meanwhile, a non-PSCI group was defined for those with MoCA-INA score ≥ 26.

**Demographic and clinical characteristics**
Demographic factors consisted of age (> 60 and ≤ 60 years old) and sex (male or female). Clinical characteristics consisted of body mass index (BMI) (obese or non-obese), hypertension (yes or no), systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes (yes or no), HbA1C, dyslipidemia (yes or no), lipid profile (the levels of triglycerides, HDL, LDL, and total cholesterol), as well as serum BDNF level at day 5 and 30 after stroke onset.

We classified the BMI based on WHO criteria for Asian population19,20 and further categorized the subjects into obese and non-obese (consisted of those with overweight and normal weight; there were no subjects with underweight). Systolic and diastolic blood pressure were measured by using sphygmomanometer performed at admission. We collected serum
BDNF level at day 5 based on prior study which revealed that BDNF was reduced at acute stroke.²¹ We also collected serum BDNF at day 30 based on another study reported that BDNF level in acute stroke would be increased steadily and reached the highest level after 30 days.²²

**Measurement of serum BDNF level**

We took the samples from patients’ serum on days 5 and 30 following the onset of the stroke. Between 7:00 and 9:00 a.m., a serum separator tube was filled with 5 mL venous whole blood from the patients. Patients were also told not to eat or drink anything for 10 hours before getting their blood drawn. Within 60 minutes of blood sampling, the venous whole blood was allowed to coagulate for 30 minutes at room temperature before being centrifuged at 1,000 × g for 15 minutes at 40°C to separate the serum and blood clot. The serum was extracted and stored at −20°C in a separate tube. The serum sample was transported to Prodia Laboratory Jakarta in a frozen state, sealed in a heat-insulated container with dry ice.

We measure the level of serum BDNF by an enzyme-linked immunosorbent assay (ELISA) using Human BDNF Immunoassay (Quantikine® R&D systems, Minneapolis, USA, Cat No: DBD00). The assay’s minimal detection limit was 20 pg/ml, and its intra- and inter-assay coefficients of variation were both less than 10%. A monoclonal antibody specific for human BDNF was pre-coated in a 96 well polystyrene microplate (BDNF, R&D System, RD1S) at a concentration of 100L in a buffered protein base with preservative and then lyophilized. The test samples were applied in duplicate (50 L/well). In duplicate wells, a standard curve was created using BDNF (R&D systems, RD1S) at concentrations of 0, 62.5, 125, 250, 500, 1000, 2000, and 4000 pg/mL. In each well, a standard, control, or sample was added and incubated for 2 hours before adding the BDNF conjugate.

Another hour was spent incubating the mixture. Each well was aspirated and washed once, then twice more for a total of three washes. Washing buffer (400 L) was used to wash each well with a squirt bottle, multi-channel pipette, manifold dispenser, or autowasher. Each well was filled with 200 mL of substrate solution and incubated at room temperature for 30 minutes, protected from light. Each well received 50 mL of Stop Solution. We lightly tapped the plate to ensure thorough mixing if the color change did not appear uniform. Using a microplate reader tuned to 450 nm, the optical density of each well was calculated in under 30 minutes.

**Statistical analysis**

We used the independent t-test, Mann-Whitney, and Chi-square test for analyzing the statistical differences between variables. We performed a receiver operating characteristics (ROC) curve analysis to determine the cut-off point of BDNF level. Bivariate analysis was conducted to analyze the relative risk of associated factors (including BDNF) between PSCI and non-PSCI group. We further performed multivariate analysis by using stepwise regression to measure factors independently associated with PSCI. All of the analyses were performed using the SPSS software version 25.0 (IBM Co. Ltd, NY, USA). A p value of < 0.05 indicated statistical significance.

**Ethical consideration**

This study has received ethical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada, Indonesia (EC No. KE/FK/0682/EC/2020). All participants were provided the information regarding the study and signed the informed consent form.

**Results**

A total of 89 patients were included in this study, with 55.1% being within the age group of more than 60 years old. Most of the participants were male (61.8%), with 68.5% having hypertension. Serum BDNF was examined on day 5 and day 30 as a prognostic factor of PSCI in stroke patients. The mean BDNF levels at day 5 and 30 were 24.54 ± 6.42 ng/mL and 24.86 ± 8.51, respectively. As much of 67.41% of patients suffered from post-stroke cognitive impairment (PSCI) during the study period. The baseline characteristics of the study participants were presented in Table 1.

Factors associated with PSCI were analyzed further as shown in Table 2. We found that age, dyslipidemia, and triglyceride levels showed a significant difference between the PSCI and non-PSCI groups (p < 0.05). Older patients had a higher risk to have PSCI compared with their younger counterparts (RR: 1.41, 95% CI: 1.03–1.94, p < 0.05). Patients with dyslipidemia were less likely to have PSCI compared with those without dyslipidemia. However, the PSCI group had a lower triglycerides level than the non-PSCI group (p < 0.05). In addition, the PSCI group had a lower MoCA-INA score than the counterpart group (p < 0.001) (Table 2).

Based on the ROC curve (Supplementary Figure 1), the cut-off points of serum BDNF level at day 5 (BDNF I) was 23.29 ng/ml and at day 30 (BDNF II) was 28.79 ng/mL. These cut-off points were then included in the bivariate analysis, and we
Table 1. Baseline characteristics.

| Parameters                              | n (%) or mean ± SD               |
|-----------------------------------------|----------------------------------|
| **Sex**                                 |                                  |
| a. Male                                 | 55 (61.8%)                       |
| b. Female                               | 34 (38.2%)                       |
| **Age, Mean ± SD, years**               | 61.03 ± 9.50                     |
| **Age group**                           |                                  |
| >60 years                               | 49 (55.1%)                       |
| ≤60 years                               | 40 (44.9%)                       |
| **BMI, Mean ± SD, kg/m²**               | 24.30 ± 3.64                     |
| **BMI categories**                      |                                  |
| a. Obese                                | 52 (58.4%)                       |
| b. Non-obese                            | 37 (41.6%)                       |
| **Hypertension**                        |                                  |
| a. Yes                                  | 61 (68.5%)                       |
| b. No                                   | 28 (31.5%)                       |
| **Systolic blood pressure (mmHg)**      | 164.12 ± 30.80                   |
| **Diastolic blood pressure (mmHg)**     | 92.15 ± 15.57                    |
| **Diabetes**                            |                                  |
| a. Yes                                  | 24 (27.0%)                       |
| b. No                                   | 65 (73.0%)                       |
| **HbA1C (%)**                           | 7.04 ± 2.19                      |
| **Dyslipidemia**                        |                                  |
| a. Yes                                  | 23 (25.8%)                       |
| b. No                                   | 66 (74.2%)                       |
| **Triglycerides level (mg/dL)**         | 174.36 ± 201.19                  |
| **HDL level (mg/dL)**                   | 41.12 ± 8.48                     |
| **LDL level (mg/dL)**                   | 137 ± 44.38                      |
| **Total cholesterol level (mg/dL)**     | 201.45 ± 70.35                   |
| **BDNF at day 5 (ng/mL)**               | 24.54 ± 6.42                     |
| **BDNF at day 30 (ng/mL)**              | 24.86 ± 8.51                     |
| **MoCA-INA score at day 5**             | 18.20 ± 6.30                     |
| **MoCA-INA score at day 30**            | 21.13 ± 5.97                     |
| **MoCA-INA score at day 90**            | 22.47 ± 5.73                     |
| **PSCI**                                |                                  |
| a. Yes                                  | 60 (67.4%)                       |
| b. No                                   | 29 (32.6%)                       |

SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BDNF, brain derived natriuretic peptide; MoCA-INA, Montreal Cognitive Assessment-Indonesia Version; PSCI, post-stroke cognitive impairment.

Table 2. Bivariate analysis of factors associated with PSCI.

| Variables                | PSCI (n = 60) | Non-PSCI (n = 29) | RR (95% CI)       | p    |
|--------------------------|---------------|-------------------|-------------------|------|
| **Demographical characteristics** |               |                   |                   |      |
| **Sex**                  |               |                   |                   |      |
| a. Female                | 41 (74.5%)    | 14 (25.5%)        | 1.33 (0.95-1.87)  | 0.06 |
| b. Male                  |               |                   |                   |      |
| **Age (years)**          | 62.7 ± 9.5    | 57.5 ± 8.7        |                   | 0.01*|
| **Age**                  |               |                   |                   |      |
| >60 years                | 38 (77.6%)    | 11 (22.4%)        | 1.41 (1.03-1.94)  | 0.02*|
| ≤60 years                | 22 (55.0%)    | 18 (45.0%)        |                   |      |
found that the mean serum BDNF level at day 5 in PSCI group was significantly lower than non-PSCI group (p < 0.001). However, there was no difference for BDNF level at day 30 in both groups. The patients with the BDNF level <23.29 ng/mL were more likely to develop PSCI (RR: 1.60, 95% CI: 1.19–2.15, p = 0.001) (Table 2).

For investigating factors that were independently associated with PSCI, we performed a multivariate analysis with stepwise regression. After adjusting by the covariates, we found that serum BDNF level at day 5 and dyslipidemia were significantly associated with PSCI. Patients with dyslipidemia were less likely to develop PSCI compared with the counterpart group (OR 0.19, 95% CI: 0.06–0.56, p < 0.05). Nevertheless, patients with day 5-BDNF level <23.29 pg/mL were five times more likely to develop PSCI compared with their counterparts (OR 5.02, 95% CI: 1.67–15.04, p < 0.05) (Table 3).

| Table 2. Continued |
|-------------------|------------------|-------------------|--------------------|-----|
| **Variables**     | **PSCI (n = 60)** | **Non-PSCI (n = 29)** | **RR (95% CI)**    | **p** |
| **Clinical examination** |                   |                   |                   |     |
| BMI (kg/m²)       | 24.1 ± 3.5        | 24.7 ± 3.9        | 0.99 (0.74-1.34)   | 0.98 |
| Obese a. Yes      | 35 (67.3%)        | 17 (32.7%)        | 0.79 (0.6-1.04)    | 0.46 |
| b. No             | 25 (67.6%)        | 12 (32.4%)        |                   |     |
| Systolic Blood Pressure (mmHg) | 162.4 ± 32.9 | 167.6 ± 25.9 | 0.46 |
| Diastolic Blood Pressure (mmHg) | 90 (60-140) | 90 (60-130) | 0.82 |
| MoCA-INA Score at day 5 | 16 (1-28) | 24 (13-29) | <0.001* |
| MoCA-INA Score at day 30 | 20 (2-28) | 25 (22-30) | <0.001* |
| MoCA-INA Score at day 90 | 21.50 (2-25) | 28 (26-30) | <0.001* |
| **Comorbidities** |                   |                   |                   |     |
| Hypertension a. Yes | 38 (62.3%) | 23 (37.7%) | 0.79 (0.6-1.04) | 0.13 |
| b. No             | 22 (78.6%)        | 6 (21.4%)         |                   |     |
| Diabetes a. Yes   | 15 (62.5%)        | 9 (37.5%)         | 0.90 (0.64-1.28)   | 0.55 |
| b. No             | 45 (69.2%)        | 20 (30.8%)        |                   |     |
| Dyslipidemia a. Yes | 9 (39.1%) | 14 (60.9%) | 0.51 (0.29-0.86) | 0.001* |
| b. No             | 51 (77.3%)        | 15 (22.7%)        |                   |     |
| **Laboratory parameters** |             |                   |                   |     |
| HbA1C (%)         | 5.95 (5.30-17.50) | 6.30 (4.60-10.60) | 0.11 |
| Triglyceride (mg/dL) | 127.50 (57-564) | 150 (77-18.29) | 0.04* |
| HDL (mg/dL)       | 40.85 (16-61)    | 41 (25-67)        | 0.96 |
| LDL (mg/dL)       | 135.50 (21-222)  | 146 (67-353)      | 0.06 |
| Total Cholesterol (mg/dL) | 193.50 (96-285) | 202 (61.80-690) | 0.16 |
| BDNF level at day 5 (pg/mL) | 22.86 ± 5.97 | 28.01 ± 5.99 | <0.001** |
| Categorization of BDNF level at day 5 a. <23.29 ng/mL | 34 (85%) | 6 (15%) | 1.60 (1.19-2.15) | 0.001* |
| b. >23.29 ng/mL   | 26 (53.1%)       | 23 (46.9%)        |                   |     |
| BDNF level at day 30 (pg/mL) | 24.42 ± 8.70 | 25.76 ± 8.19 | 0.488 |
| Categorization of BDNF level at day 30 a. <28.79 ng/mL | 45 (72.6%) | 17 (27.4%) | 1.31 (0.90-1.89) | 0.115 |
| b. >28.79 ng/mL   | 15 (55.6%)       | 12 (44.4%)        |                   |     |

PSCI, post-stroke cognitive impairment; RR, relative risk; BMI, body mass index; MoCA-INA, Montreal Cognitive Assessment-Indonesia Version; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BDNF, brain-derived natriuretic peptide.

*p < 0.05.

**p < 0.001.
Discussion

The present study demonstrated that serum BDNF level at acute phase (day 5) and dyslipidemia were associated with PSCI in first-ever acute ischemic stroke patients. Patients with BDNF level <23.29 ng/mL had a higher risk of developing PSCI, while those with dyslipidemia had a lower risk of PSCI. To our knowledge, this is the first study that demonstrated that serum BDNF could be used as a predictor for post-stroke cognitive impairment 3 months after stroke.

Our finding corroborates a prior cross-sectional study that reported that stroke survivors with cognitive impairment had a reduced level of serum BDNF and that the cognitive performance score was positively correlated with BDNF level.23 However, this study measured the level of BDNF during the post-acute phase with a median duration of illness was 10 months after stroke onset. Due to the nature of the cross-sectional study, this prior study could not suggest that BDNF can serve as a predictor for PSCI.

There are some proposed mechanisms for explaining why BDNF is associated with cognitive function in post-stroke patients. First, BDNF could increase angiogenesis, neurogenesis, and promote brain repair.24 In animal model of aging stroke, BDNF mediated facilitation of reversal learning/cognitive flexibility by inducing angiogenesis and neurogenesis which further improved the functional recovery of cognitive after stroke.24 Second, BDNF plays important roles in regulation and maintenance of synaptic plasticity. Synaptic plasticity is essential for maintaining normal cognition and attenuating brain’s resilience to recover from ischemic injury.14 BDNF involves in regulating the long-term potentiation (LTP) and long-term depression (LTD),25 as well as mediates learning and memory process in post-stroke rehabilitation.26–28

In the present study, we also found that patients with dyslipidemia had lower risk of developing PSCI. This finding is in accordance to prior study which reported that stroke survivors with dyslipidemia had a decreased risk of cognitive decline after stroke.29 The Framingham Heart Study also found similar result that high cholesterol level was associated with better cognitive function.30 However, contrary to the present study, a longitudinal study conducted in China found that increased total cholesterol and LDL were associated with cognitive impairment.31 The underlying mechanism of how dyslipidemia was associated with cognitive decline remains elusive. The interplay between dyslipidemia and cognitive function is very complex and may involve the distribution of fat mass and is influenced by age.32

The present study shows evidence that serum BDNF in acute stroke and dyslipidemia are associated with PSCI. This finding may help clinicians and researchers to predict PSCI earlier thus could prevent the worsening of cognitive function in post-stroke patients. Nevertheless, this study has some limitations. First, the sample size was small due to the participants only came from a tertiary hospital in Indonesia. Hence, the findings may not be generalized for the whole population. Second, the follow-up period was only 90 days (3 months) after stroke. Follow-up for a longer period of time will be beneficial to explore the potential role of BDNF as a solid biomarker. Moreover, we did not explore the molecular mechanisms of how reduced serum BDNF could impair cognitive function. More knowledge on this issue particularly related to the signaling pathway may be helpful in clinical and research settings.

Conclusions

Acute ischemic stroke patients with lower serum BDNF (< 23.29 ng/mL) had a higher risk of developing PSCI, while those with dyslipidemia had a lower risk of PSCI. This study suggests that BDNF could be a predictor of PSCI, allowing for earlier detection and better preventive strategies.

Data availability statement

Underlying data is available on Zenodo: https://doi.org/10.5281/zenodo.6038470.

| Variables                  | OR   | 95% CI        | p    |
|---------------------------|------|---------------|------|
| Constant                  | 0.60 | -             | 0.69 |
| BDNF at day 5 (<23.29 ng/mL) | 5.02 | 1.67-15.04    | 0.004*|
| Dyslipidemia              | 0.19 | 0.06-0.56     | 0.003*|

PSCI, post-stroke cognitive impairment; BDNF, brain derived natriuretic peptide.

*p < 0.05.
Author contributions
IS: conceptualization, methodology, validation, visualization, writing-original draft, writing-review & editing; AP: data curation, methodology, resources, supervision, funding acquisition; SS: methodology, validation, supervision; NAS: data curation, formal analysis, investigation, project administration, writing-review & editing; MH: methodology, formal analysis, software, validation, writing-review & editing; ANV: conceptualization, methodology, formal analysis, validation, visualization, writing-review & editing.

Acknowledgements
The authors would like to thank all the patients who participated in this study and all data collectors for their genuine cooperation.

References
1. Aam S, Einstad MS, Munthe-Kaas R, et al.: Post-stroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study. Front. Neurol. 2020; 11: 699. PubMed Abstract | Publisher Full Text
2. Claesson L, Lindén T, Skogø I, et al.: Cognitive impairment after stroke: Impact on activities of daily living and costs of care for elderly people. Cerebrovasc. Dis. 2005; 19: 102–109. PubMed Abstract | Publisher Full Text
3. Yang Y, Shi Y-Z, Zhang N, et al.: The disability rate of 5-year post-stroke and its correlation factors: a national survey in China. PLoS One. 2016; 11: e0165341. PubMed Abstract | Publisher Full Text
4. Prodjohardjono A, Vidyanti AN, Susianti NA, et al.: Higher level of acute serum VEGF and larger infarct volume are more frequently associated with post-stroke cognitive impairment. PLoS One. 2020; 15: e0293970. PubMed Abstract | Publisher Full Text
5. Chan SJ, Love C, Spector M, et al.: Endogenous regeneration: Engineering growth factors for stroke. Neurochem. Int. 2017; 107: 57–65. Publisher Full Text
6. Prodjohardjono A, Sutarni S, Setyopranoto I: Serum Brain-Derived Neurotrophic Factor (BDNF) Level May Predict the Functional Outcome of Acute Ischemic Stroke Patients. Biomed. Pharmacol. J. 2020; 13: 1963–1973.
7. Kermani P, Rafii D, Jin DK, et al.: Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke and vascular brain injury: Framingham study. Stroke. 2013; 44: 2768–2775. PubMed Abstract | Publisher Full Text
8. Pikula A, Beiser AS, Chen TC, et al.: Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke and vascular brain injury: Framingham study. Stroke. 2013; 44: 2768–2775. PubMed Abstract | Publisher Full Text
9. Kiprianova I, Sandkühler J, Schwab S, et al.: Brain-derived neurotrophic factor improves long-term potentiation and homeostatic synaptic plasticity: functional molecules and signaling cascades. Neural. Plast. 2020; 7342. PubMed Abstract | Publisher Full Text
10. Kiprianova I, Sandkühler J, Schwab S, et al.: Brain-derived neurotrophic factor improves long-term potentiation and homeostatic synaptic plasticity: functional molecules and signaling cascades. Neural. Plast. 2020; 7342. PubMed Abstract | Publisher Full Text
11. Schülzle R-W, Sommer C, Zoder W, et al.: Intravascular brain-derived neurotrophic factor reduces infarct size and counterregulates Bax and Bcl-2 expression after temporary focal cerebral ischemia. Stroke. 2000; 31: 2212–2217. Publisher Full Text
12. Schülzle R-W, Sommer C, Zoder W, et al.: Intravascular brain-derived neurotrophic factor reduces infarct size and counterregulates Bax and Bcl-2 expression after temporary focal cerebral ischemia. Stroke. 2000; 31: 2212–2217. Publisher Full Text
13. Wang J, Gao L, Yang Y-L, et al.: Low serum levels of brain-derived neurotrophic factor were associated with poor short-term functional outcome and mortality in acute ischemic stroke. Stroke. 2016; 47: 1943–1945. PubMed Abstract | Publisher Full Text
27. Hall J, Thomas KL, Everitt BJ: Rapid and selective induction of BDNF expression in the hippocampus during contextual learning. Nat. Neurosci. 2000; 3: 533–535. PubMed Abstract | Publisher Full Text

28. Ma Y, Wang H, Wu H, et al.: Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience. 1997; 82: 957–967. PubMed Abstract | Publisher Full Text

29. Srithumsuk W, Kabayama M, Gondo Y, et al.: The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the SONIC study. BMC Geriatr. 2020; 20: 14. PubMed Abstract | Publisher Full Text

30. Elias PK, Elias MF, D’agostino RB, et al.: Serum cholesterol and cognitive performance in the Framingham Heart Study. Psychosom. Med. 2005; 67: 24–30. PubMed Abstract | Publisher Full Text

31. Ma C, Yin Z, Zhu P, et al.: Blood cholesterol in late-life and cognitive decline: a longitudinal study of the Chinese elderly. Mol. Neurodegener. 2017; 12: 1–9.
The benefits of publishing with F1000Research:

• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com