REVIEW

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Age-related hypoxia in CNS pathology

GEORGE MIHAI BĂDESCU[1)#], MĂDĂLINA FÎLFAN[2)#], OVIDIU CIOBANU[2)], DĂNUŢ-ADRIAN DUMBRAVĂ[2)], AUREL POPA-WAGNER[2,3)]

[1)] *2nd Psychiatry Clinical Hospital, University of Medicine and Pharmacy of Craiova, Romania*

[2)] *Department of Functional Sciences, Center of Clinical and Experimental Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[3)] *Department of Psychiatry, University of Medicine Rostock, Germany*

[#]Authors with equal contribution.

Abstract

Although neuropathological conditions differ in the etiology of the inflammatory response, cellular and molecular mechanisms of neuro-inflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as "silent contributors" to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. On the other hand, acute neuroinflammation, such as in response to traumatic or cerebral ischemia, aggravates the acute damage and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. All of those sequelae impair recovery and most of them provide the ground for further cerebrovascular events and a vicious cycle develops. Therefore, understanding the mechanisms associated with vascular dementia, stroke and related complications is of paramount importance in improving current preventive and therapeutic interventions. Likewise, understanding of molecular factors and pathways associated with neuroinflammation will eventually enable the discovery and implementation of new diagnostic and therapeutic strategies indicated in a wide range of neurological conditions.

Keywords: cerebral ischemia, depression, cognition, post-stroke dementia.

Introduction

Worldwide, more than 15 million people have a stroke each year. Therefore, stroke remains one of the main causes of death and adult disability. Population aging will result in a dramatic increase in the burden of stroke. Therefore, it is not surprising that pharmaceutical industry has invested a huge amount of money in the development of pharmacotherapies of acute ischemic stroke. Promising experimental data, however, have almost consistently failed to produce a clinically effective neuroprotective drug [1–5]. Only the intravenous recombinant tissue plasminogen activator (tPA) has been approved for the treatment of acute ischemic stroke.

Co-morbidities are the major determinant in the treatment of ischemic stroke. Modifiable risk factors some of which are more common in women results from lifestyle can be modified with healthcare and medical interventions [6]. Unmodifiable risk factors serve also as markers for high stroke risk. Interestingly, the recent evidence shows that cognitive decline below dementia threshold [7] or depression [8] is associated with incidence of stroke.

The failure to consider the complexity and heterogeneity of human diseases and co-morbidities may contribute to fact that neuroprotective drugs does not work in clinical practice but do so in experimental models of stroke. Several committees (STEPS, 2009) have proposed a design framework aimed to improve the quality of preclinical stroke studies by including animals with co-morbidities. It is highly recommended that prior clinic, positive results obtained in experimental studies in young animals should be confirmed in additional studies done in aged animals and young animals models with comorbidities such as neuroinflammation, metabolic inflammation, hypertension, and hypercholesterolemia [9].

Aging, atherosclerosis, chronic inflammation and perfusion deficits

Atherosclerosis, a major risk factor for stroke and central nervous system (CNS) tissue destruction, is a disease of arteries characterized by vascular inflammation caused primarily by infiltrated monocytes into the injured vascular wall.

Several studies have suggested that inflammation may be important for accelerated progression of atherosclerosis. In a study investigating the association between inflammatory biomarkers and progression of intracranial large artery stenosis after ischemic stroke it found that in addition to traditional risk factors, circulating levels of interleukin (IL)-6 after stroke are associated with future intracranial large artery stenosis progression [10, 11]. Currently, it is widely accepted that in addition to other established cardiovascular risk factors, markers of inflammation such as C-reactive protein (CRP) is a strong predictor of subclinical and clinical atherosclerosis [12, 13] and progression of hemorrhagic stroke [14–16]. Thus, in patients with hypertension, elevated CRP levels predicted clinical events. These patients also showed a significant

relationship between clinical events and quintiles of CRP levels [12, 17, 18].

Other studies have reported on pathological vicious cycles related to CRP and atherosclerosis. For example, elevated circulating levels of CRP independently predict the development of new plaques in older persons with carotid arteries free from atherosclerotic lesions [19, 20].

However, CRP represents the strongest evidence that (neuro)inflammation is of paramount importance in a neurological syndrome such as stroke.

Virtually, all drug interventions that have been successful pre-clinically in experimental stroke have failed to demonstrate positive results in stroke patients. Our research as well as group's studies indicate that ignoring the molecular characteristics of ageing and the associated co-factors present in clinical stroke results in disappointing results in clinical trials [3, 21–23].

Studies conducted on aged rats have demonstrated that neurological impairment is more severe and functional recovery less successful than in young rats [24–26]. In addition, elderly individuals recover less well from stroke than young individuals [27, 28].

Stroke, obesity and neuroinflammation

Age represents the most important risk factor for stroke. Virtually, all drug interventions that have been successful pre-clinically in experimental stroke have failed to demonstrate positive results in stroke patients.

Our research as well as studies done in other laboratories indicate that ignoring ageing and the associated co-morbidities may lead to failure in clinical trials [3, 21–23].

Epidemiological studies have revealed an age-dependent increase of stroke susceptibility in men and women, with half of all strokes occurring in people over 75 years, and one third of cases in people over 85 years [29, 30]. Studies conducted on aged rats have demonstrated that neurological impairment is more severe and functional recovery delayed and often less successful than in young rats [24–26]. In addition, elderly individuals recover less well from stroke than young individuals [27, 28].

Stroke patients are at highest risk of death in the first weeks after the event, and between 20% to 50% die within the first month depending on type, severity, age, comorbidity and effectiveness of treatment of associated complications. Considerable spontaneous recovery occurs up to about six months. Few of the patients who survive may be left with no disability or with mild, moderate or severe disability [31, 32]. However, patients with a history of stroke are at high risk of a subsequent event, about 10% in the first year and 5% per year thereafter [33].

The obesity paradox has been reported in many articles as an inverse relationship between the body mass index (BMI) and mortality in stroke patients. However, the relationship between BMI and functional recovery in post-stroke patients has not been well described [34–39].

A cohort study from the *China National Stroke Registry* analyzed the relationship between the BMI, mortality and post-stroke functional recovery at three months after the event. This study enrolled and analyzed 10 905 eligible patients with acute ischemic stroke. Favorable behavioral recovery was seen in 52.4% of underweight (BMI 18.5 kg/m^2), 55% of normal weight (BMI 18.5–22.9 kg/m^2), 61% of overweight (BMI 23–27.4 kg/m^2), 59.2% of obese (27.5–32.4 kg/m^2) and 60.3% of severe obese (BMI >32.5 kg/m^2) stroke survivors. The overweight acute ischemic stroke survivors had a better three-month functional recovery. Remarkably, patients with obesity (BMI <32.5 kg/m^2) showed a positive outcome. However, severe obesity was associated with higher mortality while an overweight status was not a protective factor of survival at three months after stroke [40, 41].

Another study evaluating the effect of BMI on stroke rehabilitation conducted in 819 patients revealed that overweighed patients had better functional progression than non-obese patients [4, 42].

Likewise, a large retrospective cohort study from the *Danish Stroke Register* enrolling 53 812 patients has assessed the obesity paradox by analyzing the BMI, age, gender, civil status, stroke severity, stroke subtype, a pre-defined cardiovascular profile, and the socio-economic status. There was no evidence of an obesity paradox in patients with reported stroke. However, stroke occurred at a significantly younger age in patients with higher BMI [42].

Adipose tissue dysfunction in obesity contributes to chronic, low-grade inflammation that predisposes to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [43]. In obese mice, the adipose tissue is characterized by a lower interstitial oxygen partial pressure (PO_2) [44, 45]. Quite interestingly, obese patients have a lower PO_2 in the subcutaneous adipose tissue of the lateral upper arm compared with non-obese patients [46]. Furthermore, abdominal subcutaneous adipose tissue PO_2 is slightly lower in overweight/obese compared with lean subjects [47].

In conclusion, obesity could determine a worse outcome in stroke patients, yet it is not known the exact molecular pathways [4, 41, 48]. However, since obesity represents a state of chronic inflammation it is likely that this factor plays a crucial role in the general evolution of post-stroke patients.

Diabetes mellitus and metabolic inflammation

Diabetes mellitus (DM) is a great challenge for the healthcare system accounting for ~6% of global mortality in industrialized countries. Half of DM-associated deaths are attributed to cardiovascular (macro- and micro-vascular) complications.

Neuropathic complications are also frequent, occurring in about 60% of people with DM, and often overlap with, and worsen the consequences of vascular disease. Sensory neuropathy is a typical form of peripheral neuropathy characterized by an altered perception of noxious stimuli or ischemic pain. This promotes the foot ulcers caused by pressure or traumas and abrogates warning symptoms during a heart attack.

It is becoming well established that lifestyle, especially dietary habits, greatly affect metabolic health. Bad nutritional habits can lead to metabolic disorders, triggered by a system-wide chronic inflammation, also called meta-flammation, metabolic inflammation [49, 50]. A meta-flammation state can lead to a series of disorders and diseases, including hypertension, metabolic syndrome,

CVD, stroke, insulin resistance and T2DM. It is postulated that lipid hormones including sphingolipids and eicosanoids in concert with cytokines and adipokines play an important role in this process by inducing adverse regulatory responses in target cells such as macrophages. The role of genetics in driving metabolic disease development is strongly indicated by the higher concordance rate of T2DM in monozygotic than in dizygotic twins. It has been estimated that 30% to 70% of T2DM risk can be attributed to genetics [51, 52]. The investigation of gene–environment interactions through large collaborative efforts holds promise in furthering our understanding of the interplay between genetic and environmental factors [52, 53].

Since the availability of whole human genome single nucleotide polymorphisms (SNP) assays, genome-wide analysis of correlations between genetic variants (SNPs) and phenotypes has become an important approach to find disease-causative genes. Genome wide SNP typing is often performed in very large groups of human individuals (cohorts), and a large number of loci underlying disease have now been catalogued (http://www.genome.gov/gwastudies/), including variants that increase susceptibility to T2DM. However, these loci confer effects of only modest size and do not add to the clinical prediction of diabetes beyond that of traditional risk factors, such as obesity, physical inactivity, family history of diabetes, and certain clinical parameter. Furthermore, recent studies led to the identification of new genetic loci linking adipocyte and insulin biology to body fat distribution [53, 54]. The combination of genome-wide association study (GWAS) with metabolomics is breaking new grounds, as it allows making associations between SNPs and so-called intermediate phenotypes [55–57].

Metabolomics facilitates the exact quantitative measurement of large sets of lipid molecules and other metabolites, and GWAS has allowed the mapping of numerous metabolic phenotypes on the genome, as demonstrated by the discovery of substantial numbers of loci with relative strong effects [58–63]. Therefore, we could speculate diabetes mellitus is characterized by a state of increased general inflammation including at the CNS level, which might impair recovery and outcome in a wide range of neurological conditions.

Aging and neuroinflammation

Normal aging is characterized by a chronic low-grade, proinflammatory state [64, 65], with an overexpression of systemic inflammatory factors, including proinflammatory cytokines [66–68]. Age-associated inflammation in the brain manifests primarily by the chronic activation of perivascular and parenchymal macrophages/microglia expressing proinflammatory cytokines and an increased number of astrocytes [45, 69]. Given the potential role of inflammation in psychopathology, it is possible that chronically activated inflammatory signals in aging may contribute to increased vulnerability to neuropsychiatric disorders [3, 70, 71]. Inflammation in obese women is associated with increased concentrations of inflammatory markers (IL-6, CRP and adipokines) that correlated with increased symptoms of depression and anxiety [72, 73]. Conversely, removal of fat tissue surgically was associated with reduced inflammation [74, 75].

The prevalence of depression and cognitive dysfunction is particularly elevated in the elderly and obese subjects. Patients with major depression have an increased onset risk of aging-related diseases affecting the cardiovascular, cerebrovascular, neuroendocrine, metabolic, and immune systems [76–80]. Depression can thus significantly compromise successful aging defined subjectively as freedom from chronic disease and disability, along with high physical and cognitive functioning and social engagement [81, 82].

Perfusion deficits in the elderly, inflammation and depression

Recent data suggest that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation [83, 84] ultimately resulting in demyelination and neurodegeneration [22, 84].

Previous studies in rodents indicate that aging and neurodegenerative diseases promote a proinflammatory states in older individuals and leads to the development of an activated population of microglia [85–93]. Further, immune activation can be a characteristic of depression [94–96] and precipitate depressive symptoms [3, 96]. This was particularly evident in middle-aged rodents as compared to the young counterparts [97].

In the elderly, perfusion deficits can trigger microglial activation and shifts the CNS into a proinflammatory state [82–84, 90]. Recent research suggests that the inflammatory process is potentially intricately linked with multiple neurodegenerative pathways and depression and plays a central role in the pathophysiology of both depression and dementia [95, 98–104]. There is strong evidence that in human vascular disease, vascular β-amyloid (Aβ) deposition in the brain promotes development of depression and increases the risk of dementia by causing rigidity of arterioles and leading to infarction in the territory of their branching vessels in the temporal cortex of patients with cerebral amyloid angiopathy (CAA). This is associated with marked vascular and perivascular infiltration of inflammatory cells, a condition mimicked in mice subjected to chronic cerebral hypoperfusion [105–107].

Aging, neuroinflammation and depression

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant morbidity and mortality. In addition to mortality associated with suicide [108, 109], depressed patients are more likely to develop dementia, coronary artery disease and type 2 diabetes [110, 111]. Depression also complicates the prognosis of other chronic diseases [111–113]. However, biological mechanisms underlying depression remains poorly understood.

Despite advances in the treatment of major depression, one-third of depressed patients fail to respond to conventional antidepressant medication [114, 115]. One pathophysiological mechanism hypothesized to contribute to treatment resistance in depression is inflammation. Depression and dementia by a number of putative mechanisms involving neuroinflammation, oxidative stress, endothelial nitric oxide synthase uncoupling, and hyperglutamatergia, as well as neurovascular dysfunction in MDD [116, 117].

Recent evidence has shown that resistance to conventional antidepressants in major depression is associated with increased levels of inflammatory markers in the periphery including inflammatory cytokines, acute phase proteins, chemokines, and adhesion molecules [118–121]. Indeed, patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness [122]. A recent study reported that treatment-resistant depression (TRD) who has highly increased inflammation [*i.e.*, elevated baseline high-sensitivity (hs)-CRP concentration] responded preferentially to Infliximab while participants with a low level of inflammation treated with Infliximab appeared to do worse than placebo-treated participants [123]. Of note, increased inflammatory markers in depressed patients have also been associated with remitted stages of depression in response to treatment with conventional antidepressant medications [120, 121, 124–126]. On a background of systemic inflammation, proinflammatory cytokines can access the CNS and interfere with serotonin metabolism, and reduce both synaptic plasticity and hippocampal neurogenesis [94, 127]. Behavioral consequences of these effects of the immune system on the brain include depression [94, 127–129].

Cross-sectional [130–132] and prospective [133, 134] epidemiological studies have focused on peripheral inflammatory markers, such as cytokines and acute phase proteins have investigated the hypothesis that peripheral inflammatory markers are etiological factors in the development of depressive symptoms [95, 126, 135]. The most consistent finding has been the association of elevated cytokines IL-6 and IL-8 with depressive symptoms [126, 129].

Successful antidepressant treatment may reduce the level of proinflammatory markers by improving brain perfusion and by restoring the endothelial function [118, 129, 136, 137]. This, Etanercept, a soluble tumor necrosis factor-α receptor, and Celecoxib, a cyclooxygenase-2 inhibitor, and Infliximab, reduced depressive symptoms in patients with inflammatory diseases [123, 138–141].

Post-stroke depression and neuroinflammation

Recent evidence suggests that stroke and traumatic brain injury confer vulnerability to a late-onset of neuropsychiatric and neurocognitive symptoms [142, 143].

The brain responds to injuries by activation of an immunoreactive microglial population. The resulting neuroinflammation may be a possible triggering mechanism for the development of depressive-like behavior after injury that may last for weeks and months after the event [143]. Importantly, a recent meta-analysis found that the frequency of depressive symptoms even tends to increase in the long-term phase of recovery [144, 145]. Depression persists after 20 months in 34% of elderly patients with acute stroke and has been linked to a decline in cognition and unfavorable physical outcome.

Despite the fact that a high proportion of stroke patients develop mood disorders, the mechanisms underlying post-stroke depression (PSD) have so far received little attention. One major factor involved in the development of post-stroke depression could be represented by an age-related microglia activation in response to stroke. Persistent neuronal death causes a prolonged neuroinflammatory response in the infarcted area that may contribute substantially to post-stroke depression [3]. After stroke and traumatic brain injury, microglia move toward the site of damage and engulf and clear damaged cellular debris [146–149]. We have shown that aged rats showed a fulminant microglia reaction during the acute phase of stroke that persists for weeks thereafter [23, 143, 150, 151]. Since microglia has been involved in removing degenerating synapses, these findings suggest that neuroinflammation represents a significant etiopathogenic pathway.

Aging, neuroinflammation and small vessel disease

In older individuals, inflammatory mechanisms have been linked to the pathogenesis of dementia and recent evidence suggests that systemic and local neuroinflammation significantly contributes to cSVD-vascular dementia. For example, the adhesion molecules are increased in serum of patients who have white matter lesions [152, 153]. Since chronic inflammation plays an important role in hypertension, a relationship between inflammatory processes and cSVD may also be assumed [154]. One hypothesis is that these microvascular changes result in a state of chronic hypoperfusion leading gradually to oligodendrocyte death and degeneration of myelinated fibers. This may not only cause progressive white matter damage on a macroscopic scale, but also foster inflammatory processes chronically. Further, increased low-grade inflammation amplifies the risk of stroke [20] (Figure 1). However, the available data are still controversial. Thus, in a cross-sectional study investigating the possible link between biomarkers of systemic inflammation and functional status in older patients with late onset Alzheimer's disease and elderly patients with vascular dementia, it was found that IL-6 plasma levels negatively correlated with vascular dementia [2–4, 155–157].

Conclusions

Although neuropathological conditions differ in the etiology of the inflammatory response, cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as "silent contributors" to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease and subsequent dementia. On the other hand, acute neuroinflammation such as in response to traumatic or cerebral ischemia aggravates the acute damage and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. All of those sequelae impair recovery and most of them provide the ground for further cerebrovascular events, and a vicious cycle develops. Therefore, understanding the mechanisms associated with vascular dementia, stroke and related complications is of paramount importance in improving current preventive and therapeutic interventions. Likewise, understanding of molecular factors and pathways associated with neuroinflammation will eventually enable the discovery and implementation of new diagnostic and therapeutic strategies indicated in a wide range of neurological conditions.

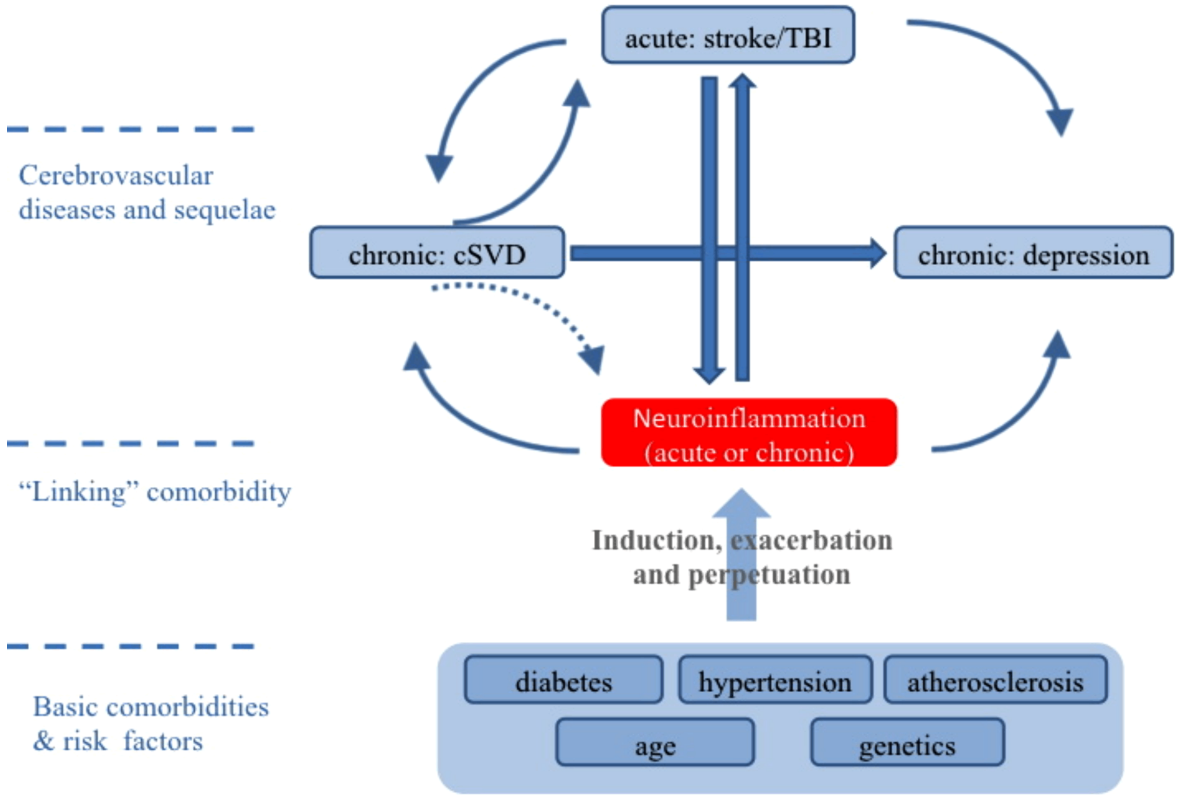

Figure 1 – ***The vicious cycle underlying cerebrovascular events and their consequences. Cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as "silent contributors" to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. Acute neuroinflammation aggravates the damage after traumatic or stroke and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. TBI: Traumatic brain injury.***

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav, 2008, 94(2):206–218.
[2] Allison DJ, Ditor DS. The common inflammatory etiology of depression and cognitive impairment: a therapeutic target. J Neuroinflammation, 2014, 11:151.
[3] Popa-Wagner A, Buga AM, Tica AA, Albu CV. Perfusion deficits, inflammation and aging precipitate depressive behaviour. Biogerontology, 2014, 15(5):439–448.
[4] Sandu RE, Buga AM, Uzoni A, Petcu EB, Popa-Wagner A. Neuroinflammation and comorbidities are frequently ignored factors in CNS pathology. Neural Regen Res, 2015, 10(9): 1349–1355.
[5] O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. Ann Neurol, 2006, 59(3):467–477.
[6] Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 stroke. Lancet, 2014, 383(9933):1973–1980.
[7] Rajan KB, Aggarwal NT, Wilson RS, Everson-Rose SA, Evans DA. Association of cognitive functioning, incident stroke, and mortality in older adults. Stroke, 2014, 45(9):2563–2567.
[8] Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth WT Jr, Sacco RL, Diez Roux AV, Alonso A. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the multi-ethnic study of atherosclerosis. Stroke, 2014, 45(8):2318–2323.
[9] Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, Lo EH; STAIR Group. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke, 2009, 40(6):2244–2250.
[10] Tousoulis D, Kampoli AM, Papageorgiou N, Androulakis E, Antoniades C, Toutouzas K, Stefanadis C. Pathophysiology of atherosclerosis: the role of inflammation. Curr Pharm Des, 2011, 17(37):4089–4110.
[11] Gencer B, Auer R, de Rekeneire N, Butler J, Kalogeropoulos A, Bauer DC, Kritchevsky SB, Miljkovic I, Vittinghoff E, Harris T, Rodondi N. Association between resistin levels and cardiovascular disease events in older adults: the health, aging and body composition study. Atherosclerosis, 2016, 245:181–186.
[12] Rizzo M, Corrado E, Coppola G, Muratori I, Novo G , Novo S. Markers of inflammation are strong predictors of subclinical and clinical atherosclerosis in women with hypertension. Coron Artery Dis, 2009, 20(1):15–20.
[13] Stancel N, Chen CC, Ke LY, Chu CS, Lu J, Sawamura T, Chen CH. Interplay between CRP, atherogenic LDL, and LOX-1 and its potential role in the pathogenesis of atherosclerosis. Clin Chem, 2016, 62(2):320–327.
[14] Di Napoli M, Parry-Jones AR, Smith CJ, Hopkins SJ, Slevin M, Masotti L, Campi V, Singh P, Papa F, Popa-Wagner A, Tudorica V, Godoy DA. C-reactive protein predicts hematoma growth in intracerebral hemorrhage. Stroke, 2014, 45(1):59–65.
[15] Di Napoli M, Godoy DA, Campi V, Masotti L, Smith CJ, Parry Jones AR, Hopkins SJ, Slevin M, Papa F, Mogoanta L, Pirici D, Popa Wagner A. C-reactive protein in intracerebral hemorrhage: time course, tissue localization, and prognosis. Neurology, 2012, 79(7):690–699.
[16] Löppönen P, Qian C, Tetri S, Juvela S, Huhtakangas J, Bode MK, Hillbom M. Predictive value of C-reactive protein for the outcome after primary intracerebral hemorrhage. J Neurosurg, 2014, 121(6):1374–1379.

[17] Rizzo M, Corrado E, Coppola G, Muratori I, Mezzani A, Novo G, Novo S. The predictive role of C-reactive protein in patients with hypertension and subclinical atherosclerosis. Intern Med J, 2009, 39(8):539–545.
[18] Seyfeli E, Sarli B, Saglam H, Karatas CY, Ozkan E, Ugurlu M. The relationship between high-sensitivity C-reactive protein levels and left ventricular hypertrophy in patients with newly diagnosed hypertension. J Clin Hypertens (Greenwich), 2015, Nov 24.
[19] Shimizu M, Ishikawa J, Yano Y, Hoshide S, Shimada K, Kario K. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. Atherosclerosis, 2011, 219(1):316–321.
[20] Molino-Lova R, Macchi C, Gori AM, Marcucci R, Polcaro P, Cecchi F, Lauretani F, Bandinelli S, Abbate R, Beghi E, Guralnik JM, Ferrucci L. High sensitivity C-reactive protein predicts the development of new carotid artery plaques in older persons. Nutr Metab Cardiovasc Dis, 2011, 21(10):776–782.
[21] Petcu EB, Smith RA, Miroiu RI, Opris MM. Angiogenesis in old-aged subjects after ischemic stroke: a cautionary note for investigators. J Angiogenes Res, 2010, 2:26.
[22] Murray KN, Buggey HF, Denes A, Allan SM. Systemic immune activation shapes stroke outcome. Mol Cell Neurosci, 2013, 53:14–25.
[23] Buga AM, Di Napoli M, Popa-Wagner A. Preclinical models of stroke in aged animals with or without comorbidities: role of neuroinflammation. Biogerontology, 2013, 14(6):651–662.
[24] Lindner MD, Gribkoff VK, Donlan NA, Jones TA. Long-lasting functional disabilities in middle-aged rats with small cerebral infarcts. J Neurosci, 2003, 23(34):10913–10922.
[25] Buchhold B, Mogoanta L, Suofu Y, Hamm A, Walker L, Kessler Ch, Popa-Wagner A. Environmental enrichment improves functional and neuropathological indices following stroke in young and aged rats. Restor Neurol Neurosci, 2007, 25(5–6):467–484.
[26] Popa-Wagner A, Buga AM, Kokaia Z. Perturbed cellular response to brain injury during aging. Ageing Res Rev, 2011, 10(1):71–79.
[27] Manwani B, Liu F, Scranton V, Hammond M, Sansing LH, McCullough LD. Differential effects of aging and sex on stroke induced inflammation across the lifespan. Exp Neurol, 2013, 249:120–131.
[28] Manwani B, Liu F, Xu Y, Persky R, Li J, McCullough LD. Functional recovery in aging mice after experimental stroke. Brain Behav Immun, 2011, 25(8):1689–1700.
[29] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation, 2012, 125(1):188–197.
[30] Willey JZ, Ortega-Gutierrez S, Petersen N, Khatri P, Ford AL, Rost NS, Ali LK, Gonzales NR, Merino JG, Meyer BC, Marshall RS. Impact of acute ischemic stroke treatment in patients >80 years of age: the specialized program of translational research in acute stroke (SPOTRIAS) consortium experience. Stroke, 2012, 43(9):2369–2375.
[31] Yu TS, Washington PM, Kernie SG. Injury-induced neurogenesis: mechanisms and relevance. Neuroscientist, 2016, 22(1):61–71.
[32] Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke, 1988, 19(12):1497–1500.
[33] Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke, 1994, 25(2):333–337.
[34] Olsen TS, Dehlendorff C, Petersen HG, Andersen KK. Body mass index and poststroke mortality. Neuroepidemiology, 2008, 30(2):93–100.
[35] Towfighi A, Ovbiagele B. The impact of body mass index on mortality after stroke. Stroke, 2009, 40(8):2704–2708.
[36] Vemmos K, Ntaios G, Spengos K, Savvari P, Vemmou A, Pappa T, Manios E, Georgiopoulos G, Alevizaki M. Association between obesity and mortality after acute first-ever stroke: the obesity-stroke paradox. Stroke, 2011, 42(1):30–36.
[37] Ovbiagele B, Bath PM, Cotton D, Vinisko R, Diener HC. Obesity and recurrent vascular risk after a recent ischemic stroke. Stroke, 2011, 42(12):3397–3402.
[38] Andersen KK, Olsen TS. Body mass index and stroke: overweight and obesity less often associated with stroke recurrence. J Stroke Cerebrovasc Dis, 2013, 22(8):e576–e581.
[39] Ryu WS, Lee SH, Kim CK, Yoon BW. Body mass index, initial neurological severity and long-term mortality in ischemic stroke. Cerebrovasc Dis, 2011, 32(2):170–176.
[40] Zhao L, Du W, Zhao X, Liu L, Wang C, Wang Y, Wang A, Liu G, Wang Y, Xu Y. Favorable functional recovery in overweight ischemic stroke survivors: findings from the China National Stroke Registry. J Stroke Cerebrovasc Dis, 2014, 23(3):e201–e206.
[41] Maysami S, Haley MJ, Gorenkova N, Krishnan S, McColl BW, Lawrence CB. Prolonged diet-induced obesity in mice modifies the inflammatory response and leads to worse outcome after stroke. J Neuroinflammation, 2015, 12:140.
[42] Burke DT, Al-Adawi S, Bell RB, Easley K, Chen S, Burke DP. Effect of body mass index on stroke rehabilitation. Arch Phys Med Rehabil, 2014, 95(6):1055–1059.
[43] Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, Jocken JW, Cajlakovic M, Ribitsch V, Clément K, Blaak EE. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. Circulation, 2011, 124(1):67–76.
[44] Rausch ME, Weisberg S, Vardhana P, Tortoriello DV. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int J Obes (Lond), 2008, 32(3): 451–463.
[45] Ye SM, Johnson RW. Increased interleukin-6 expression by microglia from brain of aged mice. J Neuroimmunol, 1999, 93(1–2):139–148.
[46] Kabon B, Nagele A, Reddy D, Eagon C, Fleshman JW, Sessler DI, Kurz A. Obesity decreases perioperative tissue oxygenation. Anesthesiology, 2004, 100(2):274–280.
[47] Pasarica M, Sereda OR, Redman LM, Albarado DC, Hymel DT, Roan LE, Rood JC, Burk DH, Smith SR. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes, 2009, 58(3):718–725.
[48] Howcroft TK, Campisi J, Louis GB, Smith MT, Wise B, Wyss-Coray T, Augustine AD, McElhaney JE, Kohanski R, Sierra F. The role of inflammation in age-related disease. Aging (Albany NY), 2013, 5(1):84–93.
[49] Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol, 2010, 72:219–246.
[50] Furuhashi M, Saitoh S, Shimamoto K, Miura T. Fatty acid-binding protein 4 (FABP4): pathophysiological insights and potent clinical biomarker of metabolic and cardiovascular diseases. Clin Med Insights Cardiol, 2015, 8(Suppl 3):23–33.
[51] Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study. Diabetologia, 1999, 42(2):139–145.
[52] Anand SS, Meyre D, Pare G, Bailey SD, Xie C, Zhang X, Montpetit A, Desai D, Bosch J, Mohan V, Diaz R, McQueen MJ, Cordell HJ, Keavney B, Yusuf S, Gaudet D, Gerstein H, Engert JC; EpiDREAM Genetics Investigators. Genetic information and the prediction of incident type 2 diabetes in a high-risk multiethnic population: the EpiDREAM genetic study. Diabetes Care, 2013, 36(9):2836–2842.
[53] Cornelis MC, Hu FB. Gene-environment interactions in the development of type 2 diabetes: recent progress and continuing challenges. Annu Rev Nutr, 2012, 32:245–259.
[54] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Mägi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Hua Zhao J, Zhao W, Chen J, Fehrmann R, Hedman ÅK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-

Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Mateo Leach I, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stančáková A, Strawbridge RJ, Ju Sung Y, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Ärnlöv J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Blüher M, Böhringer S, Bonnycastle LL, Böttcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Ida Chen YD, Clarke R, Daw EW, de Craen AJ, Delgado G, Dimitriou M, Doney AS, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, Gräßler J, Grönberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson Å, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindström J, Sin Lo K, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PK, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, Müller G, Müller-Nurasyid M, Musk AW, Nagaraja R, Nöthen MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Vernon Smith A, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundström J, Swertz MA, Swift AJ, Syvänen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q; LifeLines Cohort Study, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gådin JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JR, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, Van't Hooft FM, Vinkhuyzen AA, Westra HJ, Zheng W, Zondervan KT; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium, Heath AC, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, Ferrières J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hyppönen E, Illig T, Jacobs KB, Jarvelin MR, Jöckel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJ, Keinanen-Kiukaanniemi SM, Kiemeney LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimäki T, Lyssenko V, Männistö S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PA, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PE, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tönjes A, Trégouët DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Völker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PI, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, März W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njølstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Pérusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJ, Speliotes EK. Genetic studies of body mass index yield new insights for obesity biology. Nature, 2015, 518(7538):197–206.

[55] Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, Workalemahu T, Wu JM, Buchkovich ML, Heard-Costa NL, Roman TS, Drong AW, Song C, Gustafsson S, Day FR, Esko T, Fall T, Kutalik Z, Luan J, Randall JC, Scherag A, Vedantam S, Wood AR, Chen J, Fehrmann R, Karjalainen J, Kahali B, Liu CT, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bragg-Gresham JL, Buyske S, Demirkan A, Ehret GB, Feitosa MF, Goel A, Jackson AU, Johnson T, Kleber ME, Kristiansson K, Mangino M, Mateo Leach I, Medina-Gomez C, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Stančáková A, Ju Sung Y, Tanaka T, Teumer A, Van Vliet-Ostaptchouk JV, Yengo L, Zhang W, Albrecht E, Ärnlöv J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Blüher M, Böhringer S, Bonnet F, Böttcher Y, Bruinenberg M, Carba DB, Caspersen IH, Clarke R, Daw EW, Deelen J, Deelman E, Delgado G, Doney AS, Eklund N, Erdos MR, Estrada K, Eury E, Friedrich N, Garcia ME, Giedraitis V, Gigante B, Go AS, Golay A, Grallert H, Grammer TB, Gräßler J, Grewal J, Groves CJ, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heikkilä K, Herzig KH, Helmer Q, Hillege HL, Holmen O, Hunt SC, Isaacs A, Ittermann T, James AL, Johansson I, Juliusdottir T, Kalafati IP, Kinnunen L, Koenig W, Kooner IK, Kratzer W, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindström J, Lobbens S, Lorentzon M, Mach F, Magnusson PK, Mahajan A, McArdle WL, Menni C, Merger S, Mihailov E, Milani L, Mills R, Moayyeri A, Monda KL, Mooijaart SP, Mühleisen TW, Mulas A, Müller G, Müller-Nurasyid M, Nagaraja R, Nalls MA, Narisu N, Glorioso N, Nolte IM, Olden M, Rayner NW, Renstrom F, Ried JS, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Sennblad B, Seufferlein T, Sitlani CM, Vernon Smith A, Stirrups K, Stringham HM, Sundström J, Swertz MA, Swift AJ, Syvänen AC, Tayo BO, Thorand B, Thorleifsson G, Tomaschitz A, Troffa C, van Oort FV, Verweij N, Vonk JM, Waite LL, Wennauer R, Wilsgaard T, Wojczynski MK, Wong A, Zhang Q, Hua Zhao J, Brennan EP, Choi M, Eriksson P, Folkersen L, Franco-Cereceda A, Gharavi AG, Hedman ÅK, Hivert MF, Huang J, Kanoni S, Karpe F, Keildson S, Kiryluk K, Liang L, Lifton RP, Ma B, McKnight AJ, McPherson R, Metspalu A, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Olsson C, Perry JR, Reinmaa E, Salem RM, Sandholm N, Schadt EE, Scott RA, Stolk L, Vallejo EE, Westra HJ, Zondervan KT; ADIPOGen Consortium; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GEFOS Consortium; GENIE Consortium; GLGC; ICBP; International Endogene Consortium; LifeLines Cohort Study; MAGIC Investigators; MuTHER Consortium; PAGE Consortium; ReproGen Consortium, Amouyel P, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Brown MJ, Burnier M, Campbell H, Chakravarti A, Chines PS, Claudi-Boehm S, Collins FS, Crawford DC, Danesh J, de Faire U, de Geus EJ, Dörr M, Erbel R, Eriksson JG, Farrall M, Ferrannini E, Ferrières J, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gieger C, Gudnason V, Haiman CA, Harris TB, Hattersley AT, Heliövaara M, Hicks AA, Hingorani AD, Hoffmann W, Hofman A, Homuth G, Humphries SE,

Hyppönen E, Illig T, Jarvelin MR, Johansen B, Jousilahti P, Jula AM, Kaprio J, Kee F, Keinanen-Kiukaanniemi SM, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuulasmaa K, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimäki T, Lyssenko V, Männistö S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Möhlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Shuldiner AR, Staessen JA, Steinthorsdottir V, Stolk RP, Strauch K, Tönjes A, Tremblay A, Tremoli E, Vohl MC, Völker U, Vollenweider P, Wilson JF, Witteman JC, Adair LS, Bochud M, Boehm BO, Bornstein SR, Bouchard C, Cauchi S, Caulfield MJ, Chambers JC, Chasman DI, Cooper RS, Dedoussis G, Ferrucci L, Froguel P, Grabe HJ, Hamsten A, Hui J, Hveem K, Jöckel KH, Kivimaki M, Kuh D, Laakso M, Liu Y, März W, Munroe PB, Njølstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Pérusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sinisalo J, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Veronesi G, Walker M, Wareham NJ, Watkins H, Wichmann HE, Abecasis GR, Assimes TL, Berndt SI, Boehnke M, Borecki IB, Deloukas P, Franke L, Frayling TM, Groop LC, Hunter DJ, Kaplan RC, O'Connell JR, Qi L, Schlessinger D, Strachan DP, Stefansson K, van Duijn CM, Willer CJ, Visscher PM, Yang J, Hirschhorn JN, Zillikens MC, McCarthy MI, Speliotes EK, North KE, Fox CS, Barroso I, Franks PW, Ingelsson E, Heid IM, Loos RJ, Cupples LA, Morris AP, Lindgren CM, Mohlke KL. New genetic loci link adipose and insulin biology to body fat distribution. Nature, 2015, 518(7538):187–196.

[56] Bictash M, Ebbels TM, Chan Q, Loo RL, Yap IK, Brown IJ, de Iorio M, Daviglus ML, Holmes E, Stamler J, Nicholson JK, Elliott P. Opening up the "Black Box": metabolic phenotyping and metabolome-wide association studies in epidemiology. J Clin Epidemiol, 2010, 63(9):970–979.

[57] Kinross J, Li JV, Muirhead LJ, Nicholson J. Nutritional modulation of the metabonome: applications of metabolic phenotyping in translational nutritional research. Curr Opin Gastroenterol, 2014, 30(2):196–207.

[58] Illig T, Gieger C, Zhai G, Römisch-Margl W, Wang-Sattler R, Prehn C, Altmaier E, Kastenmüller G, Kato BS, Mewes HW, Meitinger T, de Angelis MH, Kronenberg F, Soranzo N, Wichmann HE, Spector TD, Adamski J, Suhre K. A genome-wide perspective of genetic variation in human metabolism. Nat Genet, 2010, 42(2):137–141.

[59] Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature, 2010, 466(7307): 707–713.

[60] Suhre K, Shin SY, Petersen AK, Mohney RP, Meredith D, Wägele B, Altmaier E; CARDIoGRAM, Deloukas P, Erdmann J, Grundberg E, Hammond CJ, de Angelis MH, Kastenmüller G, Köttgen A, Kronenberg F, Mangino M, Meisinger C, Meitinger T, Mewes HW, Milburn MV, Prehn C, Raffler J, Ried JS, Römisch-Margl W, Samani NJ, Small KS, Wichmann HE, Zhai G, Illig T, Spector TD, Adamski J, Soranzo N, Gieger C. Human metabolic individuality in biomedical and pharmaceutical research. Nature, 2011, 477(7362):54–60.

[61] Kettunen J, Tukiainen T, Sarin AP, Ortega-Alonso A, Tikkanen E, Lyytikäinen LP, Kangas AJ, Soininen P, Würtz P, Silander K, Dick DM, Rose RJ, Savolainen MJ, Viikari J, Kähönen M, Lehtimäki T, Pietiläinen KH, Inouye M, McCarthy MI, Jula A, Eriksson J, Raitakari OT, Salomaa V, Kaprio J, Järvelin MR, Peltonen L, Perola M, Freimer NB, Ala-Korpela M, Palotie A, Ripatti S. Genome-wide association study identifies multiple loci influencing human serum metabolite levels. Nat Genet, 2012, 44(3):269–276.

[62] Raffler J, Friedrich N, Arnold M, Kacprowski T, Rueedi R, Altmaier E, Bergmann S, Budde K, Gieger C, Homuth G, Pietzner M, Römisch-Margl W, Strauch K, Völzke H, Waldenberger M, Wallaschofski H, Nauck M, Völker U, Kastenmüller G, Suhre K. Genome-wide association study with targeted and non-targeted NMR metabolomics identifies 15 novel loci of urinary human metabolic individuality. PLoS Genet, 2015, 11(9):e1005487.

[63] Roman TS, Marvelle AF, Fogarty MP, Vadlamudi S, Gonzalez AJ, Buchkovich ML, Huyghe JR, Fuchsberger C, Jackson AU, Wu Y, Civelek M, Lusis AJ, Gaulton KJ, Sethupathy P, Kangas AJ, Soininen P, Ala-Korpela M, Kuusisto J, Collins FS, Laakso M, Boehnke M, Mohlke KL. Multiple hepatic regulatory variants at the GALNT2 GWAS locus associated with high-density lipoprotein cholesterol. Am J Hum Genet, 2015, 97(6):801–815.

[64] Bruunsgaard H, Pedersen M, Pedersen BK. Aging and proinflammatory cytokines. Curr Opin Hematol, 2001, 8(3):131–136.

[65] Elahy M, Jackaman C, Mamo JC, Lam V, Dhaliwal SS, Giles C, Nelson D, Takechi R. Blood–brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment. Immun Ageing, 2015, 12:2.

[66] Fagiolo U, Cossarizza A, Santacaterina S, Ortolani C, Monti D, Paganelli R, Franceschi C. Increased cytokine production by peripheral blood mononuclear cells from healthy elderly people. Ann N Y Acad Sci, 1992, 663:490–493.

[67] Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, Monti D, Franceschi C, Paganelli R. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol, 1993, 23(9):2375–2378.

[68] Barrientos RM, Kitt MM, Watkins LR, Maier SF. Neuroinflammation in the normal aging hippocampus. Neuroscience, 2015, 309:84–99.

[69] Jyothi HJ, Vidyadhara DJ, Mahadevan A, Philip M, Parmar SK, Manohari SG, Shankar SK, Raju TR, Alladi PA. Aging causes morphological alterations in astrocytes and microglia in human substantia nigra pars compacta. Neurobiol Aging, 2015, 36(12):3321–3333.

[70] Capuron L, Su S, Miller AH, Bremner JD, Goldberg J, Vogt GJ, Maisano C, Jones L, Murrah NV, Vaccarino V. Depressive symptoms and metabolic syndrome: is inflammation the underlying link? Biol Psychiatry, 2008, 64(10):896–900.

[71] Bartsch T, Wulff P. The hippocampus in aging and disease: from plasticity to vulnerability. Neuroscience, 2015, 309:1–16.
[72] Capuron L, Poitou C, Machaux-Tholliez D, Frochot V, Bouillot JL, Basdevant A, Layé S, Clément K. Relationship between adiposity, emotional status and eating behaviour in obese women: role of inflammation. Psychol Med, 2011, 41(7):1517–1528.
[73] Phillips CM, Perry IJ. Depressive symptoms, anxiety and well-being among metabolic health obese subtypes. Psychoneuro-endocrinology, 2015, 62:47–53.
[74] Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumié A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clément K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes, 2005, 54(8):2277–2286.
[75] Shin JA, Jeong SI, Kim M, Yoon JC, Kim HS, Park EM. Visceral adipose tissue inflammation is associated with age-related brain changes and ischemic brain damage in aged mice. Brain Behav Immun, 2015, 50:221–231.
[76] McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CW, Miranda A, Fulgosi D, Kennedy SH. Should depressive syndromes be reclassified as "metabolic syndrome type II"? Ann Clin Psychiatry, 2007, 19(4):257–264.
[77] Bauer LO. Psychiatric and neurophysiological predictors of obesity in HIV/AIDS. Psychophysiology, 2008, 45(6):1055–1063.
[78] Wolkowitz OM, Epel ES, Reus VI, Mellon SH. Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety, 2010, 27(4):327–338.
[79] Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L. Metabolic syndrome and major depression. CNS Spectr, 2014, 19(4):293–304.
[80] Martinac M, Pehar D, Karlović D, Babić D, Marcinko D, Jakovljević M. Metabolic syndrome, activity of the hypothalamic-pituitary-adrenal axis and inflammatory mediators in depressive disorder. Acta Clin Croat, 2014, 53(1):55–71.
[81] Jeste DV, Palmer BW. A call for a new positive psychiatry of ageing. Br J Psychiatry, 2013, 202:81–83.
[82] Downes CE, Crack PJ. Neural injury following stroke: are Toll-like receptors the link between the immune system and the CNS? Br J Pharmacol, 2010, 160(8):1872–1888.
[83] Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. Nature, 2010, 468(7321):253–262.
[84] Becker KJ, Kalil AJ, Tanzi P, Zierath DK, Savos AV, Gee JM, Hadwin J, Carter KT, Shibata D, Cain KC. Autoimmune responses to the brain after stroke are associated with worse outcome. Stroke, 2011, 42(10):2763–2769.
[85] Henry C, Huang Y, Wynne AM, Godbout JP. Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1β and anti-inflammatory IL-10 cytokines. Brain Behav Immun, 2009, 23(3):309–317.
[86] Palin K, Cunningham C, Forse P, Perry VH, Platt N. Systemic inflammation switches the inflammatory cytokine profile in CNS Wallerian degeneration. Neurobiol Dis, 2009, 30(1):19–29.
[87] Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. Front Behav Neurosci, 2009, 3:14.
[88] Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J Neurosci, 2005, 25(40):9275–9284.
[89] Godbout JP, Johnson RW. Age and neuroinflammation: a lifetime of psychoneuroimmune consequences. Neurol Clin, 2006, 24(3):521–538.
[90] Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol, 2008, 84(4):932–939.
[91] Townsend BE, Johnson RW. Sulforaphane induces Nrf2 target genes and attenuates inflammatory gene expression in microglia from brain of young adult and aged mice. Exp Gerontol, 2016, 73:42–48.
[92] Murray C, Sanderson DJ, Barkus C, Deacon RMJ, Rawlins JNP, Bannerman DM, Cunningham C. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol Aging, 2010, 33(3):603–616.e3.
[93] Surtees PG, Wainwright NW, Boekholdt SM, Luben RN, Wareham NJ, Khaw KT. Major depression, C-reactive protein, and incident ischemic heart disease in healthy men and women. Psychosom Med, 2008, 70(8):850–855.
[94] Maes M, Yirmyia R, Noraberg J, Brene S, Hibbeln J, Perini G, Kubera M, Bob P, Lerer B, Maj M. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab Brain Dis, 2009, 24(1):27–53.
[95] Wachholz S, Eßlinger M, Plümper J, Manitz MP, Juckel G, Friebe A. Microglia activation is associated with IFN-α induced depressive-like behavior. Brain Behav Immun, 2015, Sep 25.
[96] Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry, 2013, 18(9):963–974.
[97] Ferreira ED, Romanini CV, Mori MA, de Oliveira RM, Milani H. Middle-aged, but not young, rats develop cognitive impairment and cortical neurodegeneration following the four-vessel occlusion/internal carotid artery model of chronic cerebral hypoperfusion. Eur J Neurosci, 2011, 34(7):1131–1140.
[98] Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog Neuropsychopharmacol Biol Psychiatry, 2011, 35(3):664–675.
[99] Leonard BE. Inflammation, depression and dementia: are they connected? Neurochem Res, 2007, 32(10):1749–1756.
[100] Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol, 2011, 7(6):323–331.
[101] Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry, 2010, 68(10):930–941.
[102] Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. Pharmacol Rev, 2013, 66(1):80–101.
[103] Hellwig K, Kvartsberg H, Portelius E, Andreasson U, Oberstein TJ, Lewczuk P, Blennow K, Kornhuber J, Maler JM, Zetterberg H, Spitzer P. Neurogranin and YKL-40: independent markers of synaptic degeneration and neuroinflammation in Alzheimer's disease. Alzheimers Res Ther, 2015, 7(1):74.
[104] Freret T, Gaudreau P, Schumann-Bard P, Billard JM, Popa-Wagner A. Mechanisms underlying the neuroprotective effect of brain reserve against late life depression. J Neural Transm (Vienna), 2015, 122(Suppl 1):S55–S61.
[105] Reimer MM, McQueen J, Searcy L, Scullion G, Zonta B, Desmazieres A, Holland PR, Smith J, Gliddon C, Wood ER, Herzyk P, Brophy PJ, McCulloch J, Horsburgh K. Rapid disruption of axon–glial integrity in response to mild cerebral hypoperfusion. J Neurosci, 2011, 31(49):18185–18194.
[106] Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, Kitamura A, Washida K, Yamada M, Ito H, Tomimoto H, Takahashi R, Ihara M. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. Acta Neuropathol, 2012, 123(3):381–394.
[107] Liu Q, He S, Groysman L, Shaked D, Russin J, Scotton TC, Cen S, Mack WJ. White matter injury due to experimental chronic cerebral hypoperfusion is associated with C5 deposition. PLoS One, 2013, 8(12):e84802.
[108] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry, 2005, 62(6):593–602.
[109] Werbeloff N, Dohrenwend BP, Levav I, Haklai Z, Yoffe R, Large M, Davidson M, Weiser M. Demographic, behavioral, and psychiatric risk factors for suicide. Crisis, 2015, 23:1–8.
[110] Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia, 2006, 49(5):837–845.
[111] Loeb DF, Ghushchyan V, Huebschmann AG, Lobo IE, Bayliss EA. Association of treatment modality for depression and burden of comorbid chronic illness in a nationally representative sample in the United States. Gen Hosp Psychiatry, 2012, 34(6):588–597.

[112] Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry, 2005, 58(3):175–189.

[113] Gildengers AG, Whyte EM, Drayer RA, Soreca I, Fagiolini A, Kilbourne AM, Houck PR, Reynolds CF 3rd, Frank E, Kupfer DJ, Mulsant BH. Medical burden in late-life bipolar and major depressive disorders. Am J Geriatr Psychiatry, 2008, 16(3): 194–200.

[114] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry, 2006, 163(11): 1905–1917.

[115] Moshe H, Gal R, Barnea-Ygael N, Gulevsky T, Alyagon U, Zangen A. Prelimbic stimulation ameliorates depressive-like behaviors and increases regional BDNF expression in a novel drug-resistant animal model of depression. Brain Stimul, 2015, Nov 10.

[116] Najjar S, Pearlman DM, Devinsky O, Najjar A, Zagzag D. Neurovascular unit dysfunction with blood–brain barrier hyperpermeability contributes to major depressive disorder: a review of clinical and experimental evidence. J Neuroinflammation, 2013, 10:142.

[117] Zunszain PA, Hepgul N, Pariante CM. Inflammation and depression. Curr Top Behav Neurosci, 2013, 14:135–151.

[118] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry, 2009, 65(9):732–741.

[119] Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology, 2000, 22(4): 370–379.

[120] Papakostas GI, Shelton RC, Kinrys G, Henry ME, Bakow BR, Lipkin SH, Pi B, Thurmond L, Bilello JA. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. Mol Psychiatry, 2013, 18(3):332–339.

[121] Cubała WJ, Landowski J. C-reactive protein and cortisol in drug-naïve patients with short-illness-duration first episode major depressive disorder: possible role of cortisol immunomodulatory action at early stage of the disease. J Affect Disord, 2014, 152–154:534–537.

[122] Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatry, 2012, 83(5):495–502.

[123] Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry, 2013, 70(1):31–41.

[124] Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. Neuropsychobiology, 1997, 35(3):123–127.

[125] Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull, 2003, 37(4):133–146.

[126] Baune BT, Smith E, Reppermund S, Air T, Samaras K, Lux O, Brodaty H, Sachdev P, Trollor JN. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney Memory and Aging Study. Psychoneuroendocrinology, 2012, 37(9):1521–1530.

[127] Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. Eur J Pharmacol, 2010, 626(1): 64–71.

[128] Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther, 2011, 130(2):226–238.

[129] Dahl J, Ormstad H, Aass HC, Malt UF, Bendz LT, Sandvik L, Brundin L, Andreassen OA. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocrinology, 2014, 45:77–86.

[130] Penninx BW, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, Ferrucci L, Harris T, Pahor M. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. Biol Psychiatry, 2003, 54(5):566—572.

[131] Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. J Am Geriatr Soc, 2003, 51(8):1105–1110.

[132] Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, Hoogendijk WJ. Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord, 2008, 106(3):249–255.

[133] van den Biggelaar AH, Gussekloo J, de Craen AJ, Frölich M, Stek ML, van der Mast RC, Westendorp RG. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. Exp Gerontol, 2007, 42(7):693–701.

[134] Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. Biol Psychiatry, 2009, 65(11):973–978.

[135] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature Rev Neurosci, 2008, 9(1):46–56.

[136] Ghiadoni L, Virdis A, Magagna A, Taddei S, Salvetti A. Effect of the angiotensin II type 1 receptor blocker candesartan on endothelial function in patients with essential hypertension. Hypertension, 2000, 35(1 Pt 2):501–506.

[137] Nagata R, Kawabe K, Ikeda K. Olmesartan, an angiotensin II receptor blocker, restores cerebral hypoperfusion in elderly patients with hypertension. J Stroke Cerebrovasc Dis, 2010, 19(3):236–240.

[138] Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet, 2006, 367(9504):29–35.

[139] Kekow J, Moots RJ, Emery P, Durez P, Koenig A, Singh A, Pedersen R, Robertson D, Freundlich B, Sato R. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. Ann Rheum Dis, 2010, 69(1):222–225.

[140] Schmidt FM, Kirkby KC, Himmerich H. The TNF-*α* inhibitor etanercept as monotherapy in treatment-resistant depression – report of two cases. Psychiatr Danub, 2014, 26(3):288–290.

[141] Mehta D, Raison CL, Woolwine BJ, Haroon E, Binder EB, Miller AH, Felger JC. Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. Brain Behav Immun, 2013, 31:205–215.

[142] Alexopoulos GS. The vascular depression hypothesis: 10 years later. Biol Psychiatry, 2006, 60(12):1304–1305.

[143] Fenn AM, Gensel JC, Huang Y, Popovich PG, Lifshitz J, Godbout JP. Immune activation promotes depression 1 month after diffuse brain injury: a role for primed microglia. Biol Psychiatry, 2013, 76(7):575–584.

[144] Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke, 2005, 36(10):2296–2301.

[145] De Ryck A, Fransen E, Brouns R, Geurden M, Peij D, Mariën P, De Deyn PP, Engelborghs S. Poststroke depression and its multifactorial nature: results from a prospective longitudinal study. J Neurol Sci, 2014, 347(1–2):159–166.

[146] Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. Science, 2005, 308(5726):1314–1318.

[147] Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci, 2007, 10(11):1387–1394.
[148] Wakselman S, Béchade C, Roumier A, Bernard D, Triller A, Bessis A. Developmental neuronal death in hippocampus requires the microglial CD11b integrin and DAP12 immunoreceptor. Neurosci, 2008, 28(32):8138–8143.
[149] Ritzel RM, Patel AR, Grenier JM, Crapser J, Verma R, Jellison ER, McCullough LD. Functional differences between microglia and monocytes after ischemic stroke. J Neuroinflammation, 2015, 12:106.
[150] Badan I, Buchhold B, Hamm A, Gratz M, Walker LC, Platt D, Kessler Ch, Popa-Wagner A. Accelerated glial reactivity to stroke in aged rats correlates with reduced functional recovery. J Cereb Blood Flow Metab, 2003, 23(7):845–854.
[151] Esposito E, Mandeville ET, Hayakawa K, Singhal AB, Lo EH. Effects of normobaric oxygen on the progression of focal cerebral ischemia in rats. Exp Neurol, 2013, 249:33–38.
[152] de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain, 2002, 125(Pt 4):765–772.
[153] Hinman JD, Lee MD, Tung S, Vinters HV, Carmichael ST. Molecular disorganization of axons adjacent to human lacunar infarcts. Brain, 2015, 138(Pt 3):736–745.
[154] Schiffrin EL. Inflammation, immunity and development of essential hypertension. J Hypertens, 2014, 32(2):228–229.
[155] Zuliani G, Guerra G, Ranzini M, Rossi L, Munari MR, Zurlo A, Blè A, Volpato S, Atti AR, Fellin R. High interleukin-6 plasma levels are associated with functional impairment in older patients with vascular dementia. Int J Geriatr Psychiatry, 2007, 22(4):305–311.
[156] Androsova LV, Mikhaïlova NM, Zozulia SA, Dupin AM, Rassadina GA, Lavrent'eva NV, Kliushnik TP. Inflammatory markers in Alzheimer's disease and vascular dementia. Zh Nevrol Psikhiatr Im S S Korsakova, 2013, 113(2):49–53.
[157] Popa-Wagner A, Pirici D, Petcu EB, Mogoanta L, Buga AM, Rosen CL, Leon R, Huber J. Pathophysiology of the vascular wall and its relevance for cerebrovascular disorders in aged rodents. Curr Neurovasc Res, 2010, 7(3):251–267.

Corresponding author
Aurel Popa-Wagner, Professor, PhD, Department of Psychiatry, University of Medicine Rostock, Gehlsheimer Straße 20, D–18147 Rostock, Germany; Phone +49–381–494–9686, Fax +49–381–494–9639, e-mail: aurel.popa-wagner@med.uni-rostock.de

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