Neurological Sciences (2019) 40:1901–1907
https://doi.org/10.1007/s10072-019-03907-2

ORIGINAL ARTICLE

BDNF Val66Met polymorphism and cognitive impairment in Parkinson's disease—a meta-analysis

Yanying Yin[1] · Xuening Su[1] · Lishou Pan[2] · Chen Li[1]

Received: 30 December 2018 / Accepted: 16 April 2019 / Published online: 18 May 2019

Abstract

Background Conflicting results identifying the association between Brain-derived neurotrophic factor (BDNF) polymorphism, Val66Met, and cognitive impairment in Parkinson's disease (PD) have been reported.

Methods and results To clarify whether Val66Met is related to cognitive impairment in PD, we carried out this meta-analysis by searching literature from PubMed, Web of Science, and Embase databases regarding this polymorphism. Six eligible studies involving 1467 PD patients were included in this meta-analysis. Our results showed statistically significant association between Val66Met and risk of cognitive impairment in PD patients in additive model (Met/Met vs. Val/Val: OR 3.82, 95%CI 1.32 to 11.08, $p = 0.01$) and recessive model (Met/Met vs. Val-carrier: OR 3.81, 95%CI 1.38 to 10.53, $p = 0.01$) except for dominant model.

Conclusions Our meta-analysis implicates Val66Met BDNF polymorphism may be associated with Parkinson's disease cognitive impairment, further well-designed studies with larger populations are required to validate these results owing to the limited research.

Keywords BDNF · Polymorphism · PD-related cognitive impairment · Meta-analysis

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by disabling motor (tremor, bradykinesia, rigidity, and postural instability) and nonmotor (e.g., sleep, mood, and cognitive disturbances) symptoms. Cognitive impairment is one of the most common neuropsychiatric manifestations of PD, especially in the late stage. It is considered a predictor for dementia, which greatly affects functioning and quality of life and costs on patients, caregivers, and society [1–3]. The pathophysiology of PD-related cognitive impairment and dementia is still unknown. Currently, some general features such as severity of PD, in particular gait and postural disturbances, age onset PD, and dopaminergic deficits, have been found to be associated with PD-related cognitive impairment [4–7]. Published studies have suggested a genetic contribution to PD-dementia predisposition, evidenced in a family history of the disease [8]. So, it is believed that environmental and genetic factors contribute for the development of this symptom [8]. More recently, genes involved in neuroplasticity have been investigated in association with cognitive functions with interesting results [9–16].

The gene encoding brain-derived neurotrophic factor (BDNF) is interesting in this respect, as its product is widely distributed throughout the brain and is especially important for survival and differentiation of dopaminergic neurons in the basal ganglia [17, 18]. BDNF has been also shown to act as a modulating role in synaptic plasticity after the nervous system has matured [19] and to interact with dopamine receptor stimulation in the fronto-striatal circuitry, with alteration of cognition in PD [16]. A functional polymorphism, Val66Met, localized in the BDNF has been found to be associated with in PD-related cognitive impairment [10–15], but the results were controversial. To clarify whether Val66Met is related to PD cognitive impairment risk, we performed this meta-analysis, aiming to identify the contribution of Val66Met to PD-related cognitive impairment pathogenesis and to illustrate possible reasons for these conflicting results.

Yanying Yin and Xuening Su contributed equally to this work.

✉ Chen Li
lichenneuron@163.com

[1] Department of Neurology, The Fifth Central Hospital of Tianjin, 40 Zhe jiang Road of Binhai New Area, Tianjin 300450, People's Republic of China

[2] Department of Neurology, The People's Hospital of Yichun City, Yichun University, 88 West Zhong Shan Road, Yichun, Jiangxi Province 336000, People's Republic of China

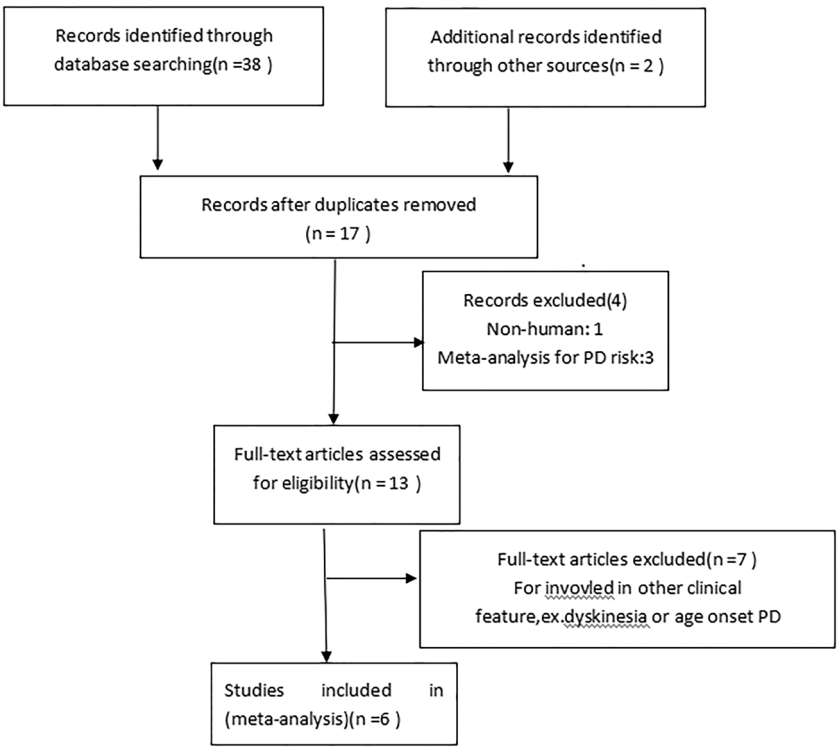

Fig. 1 Six eligible studies (1467 PD patients)

Methods

Literature search strategy

We searched the PubMed, Web of Science, and Embase databases for studies, with keywords including "Parkinson's disease or PD cognitive impairment" and "Val66Met OR rs6265 OR G196A". Last literature search was conducted on August 5, 2018. To identify studies that may have been missed by the database search, reference lists of all articles that met the inclusion criteria and of relevant review articles were examined.

Selection and exclusion criteria

Included studies should meet the following criteria: (1) studies on the relationship between BDNF polymorphism and PD cognitive impairment or PD clinical features, (2) using of a case-control design, (3) studies with full text articles, (4) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI), and (5) genotype distribution of control population was in Hardy-Weinberg equilibrium (HWE). Reviews, abstracts from conferences, republished or duplicate studies, and studies with insufficient information for data extraction were excluded.

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Study outcomes	Sample size (PD)	Asso (Y/N)
Guerini FR	2009	Italy	Caucasians	CI/NCI	294	Y
Gao L	2010	Spain	Caucasians	CI/NCI	193	N
Białecka M	2014	Polish	Caucasians	CI/NCI	244	N
Altmann V	2016	Brazil	Caucasians	CI/NCI	175	Y
Svetel M	2013	Belgrade	Caucasians	MMSE	177	N
VanderKolk NM	2014	Netherlands	Caucasians	MMSE	384	N
Altmann V	2016	Brazil	Caucasians	MMSE	175	Y

IC cognitive impairment of Parkinson's disease, *NCI* no cognitive impairment of PD patients, *Asso* association between theVal66Met BDNF polymorphism and Parkinson's disease cognitive impairment

Table 2 The distribution of BDNF Val66Met polymorphism in cognitive impairment and no cognitive impairment of PD patients

Author	Year	CI/NCI		
		Val/Val	Val/Met	Met/Met
Guerini FR	2009	12/145	10/106	7/14
Gao L	2010	14/85	8/67 (Met-carrier)	–
Białecka M	2014	143/33	47/15	5/1
Altmann V	2016	56/61	38/20 (Met-carrier)	–

Data extraction

Data from eligible studies were extracted independently by two investigators, and discrepancies were resolved by discussion with a third reviewer. The following information was extracted: (1) first author and publication year, (2) country and ethnicity, (3) sample size, (4) genotype in cognitive impairment and no cognitive impairment patients, and (5) MMSE scores according to BDNF genotypes.

Statistical analysis

Associations between Val66Met of BDNF and risk of PD-related cognitive impairment were calculated by odds ratios (OR) and 95% confidence intervals (CI). Continuous outcomes for MMSE scores between different genotypes were calculated standardized mean difference (SMA). A pooled OR or SMA and 95%CI were calculated by the Z test to evaluate this association under the dominant (Met carrier vs. Val/Val), recessive (Met/Met vs. Val carrier), and additive (Met/Met vs. Val/Val) genetic models. Heterogeneity among studies was evaluated using the Q test and was quantified using I^2 ($p < 0.10$ and $I^2 > 50\%$ indicated evidence of heterogeneity). The ORs or SMA were pooled through a fixed effects model when no heterogeneity was observed among studies. Otherwise, a random effects model was adopted. Publication bias was assessed by Begg's and Egger's tests. $P < 0.05$ was considered significant for all tests. All above statistical analysis was performed using Stata 12.0 (http://www. Stata. com).

Results

Characteristics of published studies

A total of 17 potentially eligible articles were identified after removing duplicates. Then, four articles were excluded because the object of the study is not human ($n = 1$), three meta-analysis for the association between Val66Met of BDNF and PD risk ($n = 3$). After eliminating the four articles mentioned above, the remaining 13 were read in full and seven are excluded because the study designs are for other clinical feature, for example, dyskinesia or age onset PD, not involving the cognitive impairment. Finally, 6 eligible studies (1467 PD patients) were chosen, and the data were extracted (Fig. 1). The main characteristics of them are summarized in Tables 1, 2, and 3. Four studies involved the incidence of PD-related cognitive and non-cognitive impairment in different BDNF genotypes, and three studies referred to the MMSE scores of patients with different BDNF genotypes in these six studies. The MMSE scores of different genotypes and the incidence of PD-related cognitive impairment of different genotypes were studied simultaneously in Altmann V's research [15]. In Gao L's and Altmann V's studies, cases with Met/Val or Met/Met genotype were pooled together due to the small sample size with Met/Met genotype [11, 15]. So, the Met allele was unaccounted.

Meta-analysis of Val66Met

Overall, heterogeneity in the additive model and recessive model was not statistically significant, and the ORs and 95% CIs were therefore calculated in fixed-effect model. Otherwise, in dominant model and comparison of continuous outcomes for the MMSE scores, the heterogeneity test revealed obvious heterogeneity among studies, so the random-effect model was used (Tables 3 and 4). The meta-analysis suggests that Val66Met was significantly associated with an increased PD-related cognitive impairment risk in additive and recessive models not in dominant model in Caucasians (Table 4, Fig. 2a–c). Pooled SMA showed that there was no significant difference among the BDNF Met carrier and Val/Val genotypes ($P = 0.63$) on MMSE scores (Table 3, Fig. 2d).

Table 3 The MMSE scores of patients according to BDNF genotypes

Author	Year	BDNF Met carrier (mean (±standard deviation))	BDNF Val/Val (mean (±standard deviation))	P (meta)	Begg's test (*P*)	Egger's test (*P*)
Svetel M	2013	28.5(1.9)	27.9(3)	0.63(random model)	1.00	0.81
VanderKolk NM	2014	28(1.6)	28(1.6)			
Altmann V	2016	23.3(4.3)	25.1(3.8)			

Table 4 Meta-analysis of BDNF Val66Met polymorphism and risk of cognitive impairment in PD

Genetic model	P_Q	I^2	OR	95%CI	P_Z	Calculated model	Begg's test (*P*)	Egger's test (*P*)
Additive model	0.00	45.9%	3.82	1.32–11.08	0.01	fix	1.00	–
Recessive model	0.20	37.9%	3.81	1.38–10.53	0.01	fix	1.00	–
Dominant model	0.09	53.5%	1.21	1.08–3.97	0.49	random	0.73	0.61

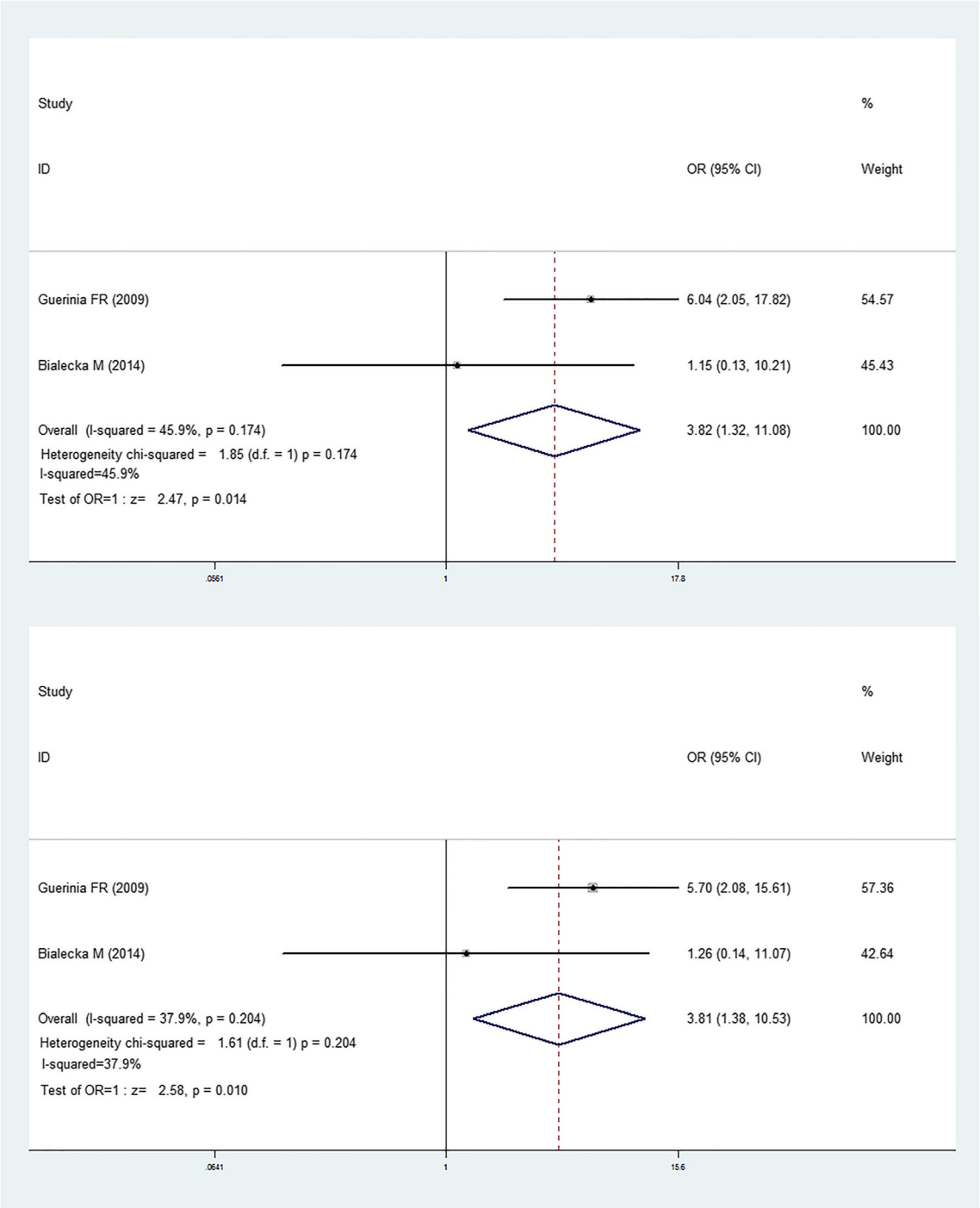

Fig. 2 An increased PD-related cognitive impairment risk in additive and recessive models not in dominant model in Caucasians

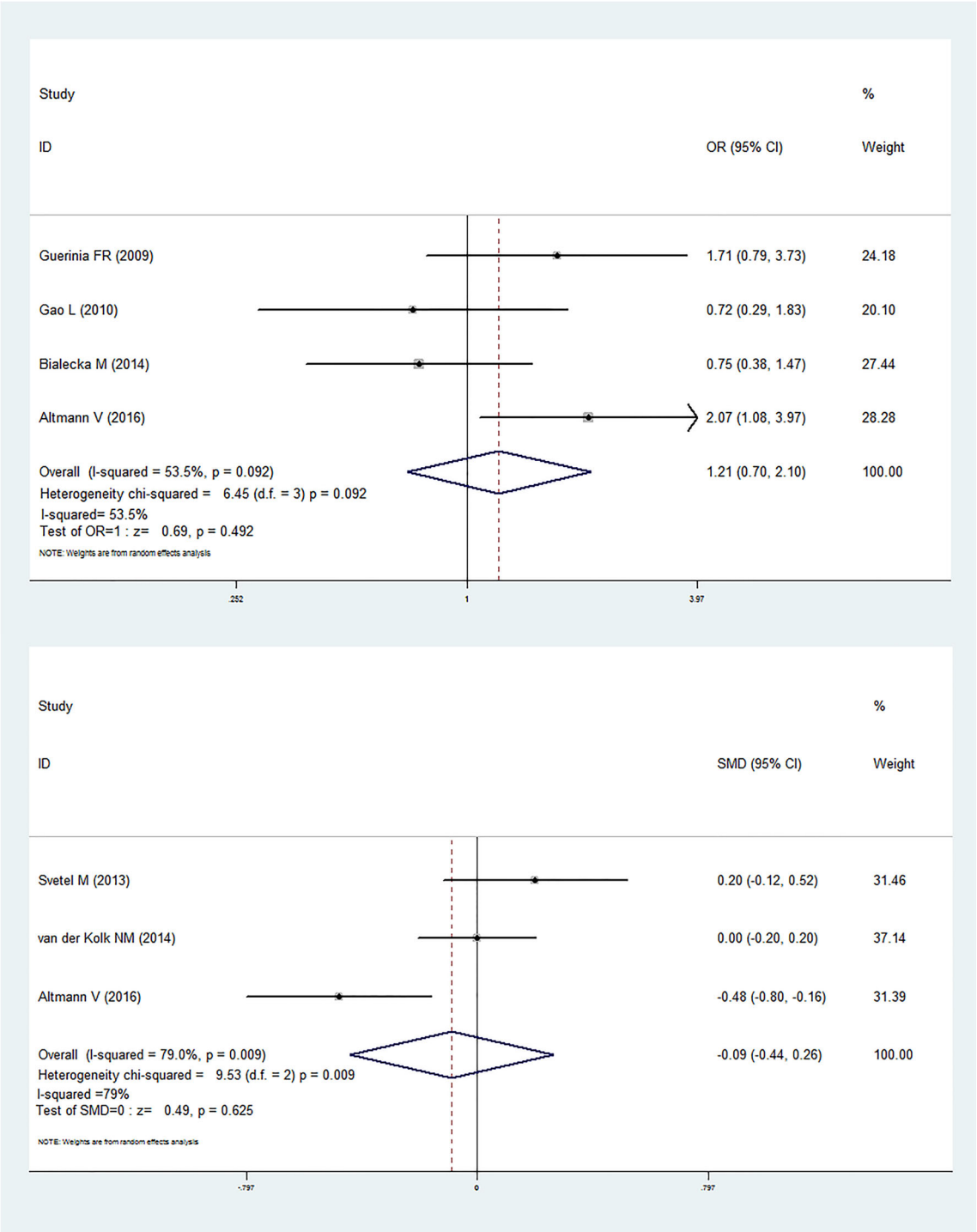

Fig. 2 (continued)

Assessment of publication bias and sensitivity analysis

Significant risk of publication bias was not observed in Egger's test or Begg's test (Tables 3 and 4). Sensitivity analysis in dominant model showed that none of the studies on its own significantly influenced the results.

Discussion

Val66Met (rs6265) polymorphism is located in the terminal exon of the BDNF gene. The presence of the minor allele (Met) of this polymorphism causes an altered intracellular distribution and a reduced activity-induced secretion of the BDNF protein in neurons [20, 21]. BDNF which is widely expressed

in the central nervous system is important for growth, survival, and neuronal cell differentiation in the central nervous system [17, 18] and plays a role as neuromodulator in neurological (cognitive and motor) activities [19]. The involvement of BDNF in cognitive processes is supported by the association of Val66Met polymorphism with abnormal hippocampal function, poor episodic memory [20], reduced hippocampal volume [22], and variation in cortical morphology [23] in healthy subjects. Recently, studies of BDNF Val66Met polymorphism in PD-related cognitive impairment increased gradually; however, the results were controversial.

Guerini FR et al. found that the BDNF (AA) genotype was associated to a sixfold risk of cognitive impairment in PD patients using the logistic regression analysis model [10]. Altmann V et al. showed that BDNF 66Met carriers presented mean lower MMSE scores (1.9 points) when compared to Val/Val homozygous subjects ($p = 0.005$). Cognitive impairment was associated with presence of at least one Met allele ($p = 0.036$) in univariate analysis. After controlling for gender, ancestry, disease duration, and disease severity, the BDNF 66Met allele was still associated with cognitive impairment in PD ($p = 0.005$, RR = 1.45,95%CI = [1.1–1.8]) [15]. In adverse, Gao L et al. reported that no association was detected between this genetic variant and any clinical feature including cognitive dysfunction in univariate and multivariate analyses [11]. None of the variants of the studied polymorphisms was associated with cognitive status in demented PD and non-demented PD in Białecka M'study; interestingly, they found that the BDNFMet/Met + Val/Met subgroup performed slightly better in terms of delayed recall [14]. The results from both Svetel M and VanderKolk NM's studies revealed that there was no statistically significant difference in MMSE scores between the BDNF Met carrier and Val/Val groups [12, 13]. This discrepancy about genetic factors linked to PD-related cognitive impairment should not be surprising, given that PD-related cognitive impairment is a complex disease associated with genetic and environmental risk factors, for instance, age and disease severity. Another reason is that the different definition of the PD-related cognitive impairment may contribute to the different results in the above studies. In Guerini FR's study, the cognitive impairment was defined as MMSE ≤ 24 score; for other studies, it is not mentioned how to define cognitive impairment. As all the above studies explored the association between Val66Met and PD-related cognitive impairment risk in Caucasians, so we mainly focused on Caucasians.

Significant association of Val66Met with risk of cognitive impairment in PD was found in the pooled Caucasian population under the additive and recessive models not in dominant model. In addition, an interesting question was that no statistical difference of MMSE scores was observed between the BDNF Met carrier and BDNF Val/Val, for the reason of this problem may be that the included studies compared MMSE scores in the Met carrier VS. Val/Val not Met/Met vs. Val carrier as mentioned above the additive or recessive models.

While our meta-analysis offers the first comprehensive assessment of Val66Met polymorphism and risk of cognitive impairment of PD, the results should be interpreted with caution in light of several limitations. One is that we only analyzed Caucasians not in other ethnic population. Another limitation is that we could not perform multivariate regression analysis based on age, disease severity gender, and phenotype of PD due to limited data reporting. In addition, in dominant model, four studies' data were available; however, there were only two studies' data available in the additive and recessive models, so the result should be cautiously treated due to the limited data under the additive and recessive models.

Our results suggest that the homozygote Val66Met may be associated with increased risk of cognitive impairment of PD, at least among Caucasians. However, future studies should verify our findings in larger populations, particularly in other ethnicities in multivariate regression analysis model for excluding the effect of confounding factors such as age, disease severity, and gender. In addition, this polymorphism of BDNF should be studied in different phenotype of PD patients (presenting tremor dominant or postural instability gait disorders) with cognitive impairment which may better guide clinical treatments and judge the prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386:896–912
2. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA (2007) Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130:1787–1798
3. Papagno C, Trojano L (2018) Cognitive and behavioral disorders in Parkinson's disease: an update. I: cognitive impairments. Neurol Sci 39:215–223
4. Jokinen P, Brück A, Aalto S, Forsback S, Parkkola R, Rinne JO (2009) Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat Disord 15:88–93
5. Aleksovski D, Miljkovic D, Bravi D, Antonini A (2018) Disease progression in Parkinson subtypes: the PPMI dataset. Neurol Sci 39:1971–1976
6. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ (2010) Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain 133:1755–1762
7. Dujardin K, Leentjens AF, Langlois C, Moonen AJ, Duits AA, Carette AS, Duhamel A (2013) The spectrum of cognitive disorders in Parkinson's disease: a data-driven approach. Mov Disord 28:183–189

8. Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 9:1200–1213
9. Teixeira AL, Barbosa IG, Diniz BS, Kummer A (2010) Circulating levels of brain-derived neurotrophic factor: correlation with mood, cognition and motor function. Biomark Med 4:871–887
10. Guerini FR, Beghi E, Riboldazzi G, Zangaglia R, Pianezzola C, Bono G, Casali C, Di Lorenzo C, Agliardi C, Nappi G, Clerici M, Martignoni E (2009) BDNF Val66Met polymorphism is associated with cognitive impairment in Italian patients with Parkinson's disease. Eur J Neurol 16(11):1240–1245
11. Gao L, Díaz-Corrales FJ, Carrillo F, Díaz-Martín J, Caceres-Redondo MT, Carballo M, Palomino A, López-Barneo J, Mir P (2010) Brain-derived neurotrophic factor G196A polymorphism and clinical features in Parkinson's disease. Acta Neurol Scand 122(1):41–45
12. Svetel M, Pekmezovic T, Markovic V, Novaković I, Dobričić V, Djuric G, Stefanova E, Kostić V (2013) No association between brain-derived neurotrophic factor G196A polymorphism and clinical features of Parkinson's disease. Eur Neurol 70:257–262
13. van der Kolk NM, Speelman AD, van Nimwegen M, Kessels RP, IntHout J, Hakobjan M, Munneke M, Bloem BR, van de Warrenburg BP (2015) BDNF polymorphism associates with decline in set shifting in Parkinson's disease. Neurobiol Aging 36: 1605.e1–1605.e6
14. Białecka M, Kurzawski M, Roszmann A, Robowski P, Sitek EJ, Honczarenko K, Mak M, Deptuła-Jarosz M, Gołąb-Janowska M, Droździk M, Sławek J (2014) BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. Neurosci Lett 561:86–90
15. Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CR, Hutz MH (2016) Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. Neurosci Lett 615:88–91
16. Foltynie T, Lewis SG, Goldberg TE, Blackwell AD, Kolachana BS, Weinberger DR, Robbins TW, Barker RA (2005) The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. J Neurol 252(7):833–838
17. Baydyuk M, Russell T, Liao GY, Zang K, An JJ, Reichardt LF, Xu B (2011) TrkB receptor controls striatal formation by regulating the number of newborn striatal neurons. Proc Natl Acad Sci U S A 108(4):1669–1674
18. Hyman C, Hofer M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP, Lindsay RM (1991) BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350: 230–232
19. McAllister AK, Katz LC, Lo DC (1999) Neurotrophins and synaptic plasticity. Annu Rev Neurosci 22:295–318
20. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112(2):257–269
21. Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS (2004) Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J Neurosci 24(18):4401–4411
22. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK (2006) BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol Psychiatry 59:812–815
23. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR (2004) The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 24:10099–10102