CUSBED 2021 (6)2: 112-119
doi.org/10.51754/cusbed.948015

Cumhuriyet Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi
Journal of Cumhuriyet University Health Sciences Institute

Investigation of Plasma PGC1-α, Irisin, BDNF, GAL, and GALP Levels in Parkinson's Disease

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Received	Accepted	Published
04.06.2021	17.06.2021	30.08.2021

Abstract: The roles of novel peptides such as transcription cofactor peroxisome proliferator 1-alpha, irisin, brain-derived neurotrophic factor, galanin and galanin-like peptide in Parkinson's disease are not fully known. This study, plasma levels of the novel peptides that may affect the pathophysiology of Parkinson's disease were examined. The study was conducted as a cross-sectional. The study consisted of two groups, including 45 newly diagnosed patients with idiopathic Parkinson's disease and 45 healthy individuals. The peptide levels in plasma samples collected from the groups were measured by the ELISA method. The means ages of both groups were over 65 years old and the age difference was insignificant. When plasma proliferator 1-alpha, irisin, brain-derived neurotrophic factor, galanin, and galanin-like peptide levels between the groups were examined, it was determined that the median levels of the patient group (3.38[2.60-4.43]ng/mL, 12.77[9.70-15.04]ng/mL, 1.61[1.35-2.01]ng/mL, 15.46[12.98-17.77]ng/L, and 47.68[32.5-65.86]pg/mL, respectively) were lower compared to the control group (5.98[4.99-7.03]ng/mL, 18.77[15.01- 20.53]ng/mL, 4.39[3.70-4.95]ng/mL, 21.32[16.70-25.87]ng/L, and 48.92[28.66-69.68]pg/mL, res-pectively). While significant positive low correlations were found between plasma brain-derived neurotrophic factor levels and galanin and irisin, significant positive moderate correlations were found between plasma PGC1-α levels and BDNF, irisin and GAL. A significant negative correlation was found between age and brain-derived neurotrophic factor levels. As far as we know, the study is the first report in the literature in which the aforementioned peptides associated with Parkinson's disease were examined together. We consider that more detailed studies are needed to shed light on the roles and mechanisms of these peptides in Parkinson's disease.

Keywords: Parkinson's Disease, peroxisome proliferator 1-alpha, irisin, brain-derived neurotrophic factor, galanin, galanin-like peptide

Parkinson Hastalığında Plazma PGC1-α, İrisin, BDNF, GAL ve GALP Düzeylerinin İncelenmesi

Özet: Transkripsiyon kofaktör peroksizom proliferatör 1-alfa, irisin, beyin kaynaklı nörotrofik faktör, galanin ve galanin benzeri peptit (GALP) gibi yeni peptitlerin Parkinson Hastalığı'ndaki rolleri, tam olarak bilinmemektedir. Bu çalışmada, Parkinson Hastalığı'nın patofizyolojisini etkileyebilecek yeni peptitlerin plazma seviyeleri incelendi. Bu çalışma kesitsel olarak gerçekleştirilmiştir. Çalışma, 45 yeni tanı almış idiyopatik Parkinson hastası ve 45 sağlıklı birey olmak üzere iki gruptan oluşturuldu. Gruplardan toplanan plazma örneklerindeki peptit seviyeleri ELISA yöntemi ile ölçüldü. Her iki grubun yaş ortalaması 65 yaşın üzerinde ve gruplar arasındaki yaş farkı istatistiksel olarak anlamsızdı. Gruplar arasındaki plazma peroksizom proliferatör 1-alfa, irisin, beyin kaynaklı nörotrofik faktör, galanin ve galanin benzeri peptit median düzeyleri incelendiğinde; kontrol grubuna (sırasıyla 5.98 [4.99-7.03] ng/mL, 18.77 [15.01- 20.53] ng/mL, 4.39 [3.70-4.95] ng/mL, 21.32 [16.70-25.87] ng/L ve 48.92 [28.66-69.68] pg/mL) göre, hasta grubunda median düzeylerinin (sırasıyla 3.38 [2.60-4.43] ng/mL, 12.77 [9.70-15.04] ng/mL, 1.61 [1.35-2.01] ng/mL, 15.46 [12.98-17.77] ng/L ve 47.68 [32.5-65.86] pg/mL) düşük olduğu tespit edildi (peroksizom proliferatör 1-alfa düzeyleri için $p<0.01$, galanin benzeri peptit için $p>0.05$, diğer peptit düzeyleri için $p<0.05$). Plazma beyin kaynaklı nörotrofik faktör düzeyleri ile galanin ve irisin arasında pozitif yönde anlamlı düşük korelasyonlar (sırasıyla, $r=0.348$; $p=0.001$, $r=0.271$; $p=0.011$), plazma peroksizom proliferatör 1-alfa düzeyleri ile beyin kaynaklı nörotrofik faktör, irisin ve galanin arasında ise pozitif yönde anlamlı orta düzeyde korelasyonlar saptandı (sırasıyla, $r=0.685$, $r=0.424$ ve $r=0.532$; p değerleri tümü için $p\leq0.001$). Yaş ile beyin kaynaklı nörotrofik faktör düzeyleri arasında ise negatif anlamlı korelasyon bulundu ($p=0.040$; $r=-0.225$). Bu çalışma bildiğimiz kadarıyla PH ile ilişkili bahsi geçen peptidlerin birlikte incelendiği literatürdeki ilk rapordur. Bu peptidlerin Parkinson Hastalığı'daki rollerinin ve mekanizmalarının aydınlatılması adına gelecekte daha detaylı çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar Kelimeler: Parkinson Hastalığı, peroksizom proliferatör 1-alfa, irisin, beyin kaynaklı nörotrofik faktör, galanin, galanin benzeri peptit

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INTRODUCTION

Parkinson's disease (PD) was first described as the shaking palsy in 1807 by the English scientist James Parkinson (Parkinson, 2002). Prevalence studies show that approximately 1% of the population over the age of 65 is affected by this disease (Akbayır et al., 2017). The underlying causes of neuronal loss in Parkinson's disease are not known exactly, and it is considered that factors such as oxidative stress, inflammation, glutamate toxicity, microglial cell activity, apoptosis, excess nitric oxide production, mitochondrial dysfunction, environmental and genetic factors may cause it (Dias et al., 2013).

Transcription cofactor peroxisome proliferator 1-alpha (PGC1-α) is a transcriptional co-regulator with various functions, including mitochondrial biogenesis in tissues such as the liver, heart, brain, and kidney (Cheng et al., 2012). PGC1-α, which occurs as a link between mitochondrial dysfunction and transcriptional dysregulation in neurodegenerative diseases, is the first member of the PGC1 family and was defined at the end of the 1990s (Bost and Kaminksi, 2019). Moreover, energy metabolism has been described as a modulator of insulin signal and is considered to be associated with neurodegenerative disorders, including Alzheimer's, Huntington's disease, and PD (Agarwal et al., 2017).

Irisin was first described by Boström et al. in 2012. Irisin, which is involved in the formation of brown adipose tissue from white adipose tissue, is largely secreted in the muscle tissue and the brain (Jin et al., 2018). Although the exact mechanisms and etiopathogenesis that reveal the correlation between Parkinson's disease and irisin have not been fully understood yet, the role of irisin in neurodegeneration is an important issue that needs to be clarified. It is considered that the changes in the regulation of neurotrophic factors and their receptors are associated with neurodegenerative diseases and that brain-derived neurotrophic factor (BDNF) supports neuronal proliferation by preventing cell death and thus plays a role in the pathogenesis of diseases such as Alzheimer's and Parkinson's disease (Palasz et al., 2020). Neurotrophins are effective for neuronal development (Zhao et al., 2017). It is known that these effects of neurotrophins are associated with decreased BDNF mechanism in the substantia nigra pars compacta, a vulnerable region in significant neuronal loss (Yang et al., 2020).

Galanin (GAL) is a 29-amino acid peptide (30 amino acids in humans) isolated from the porcine intestine in 1983 (Tatemoto et al., 1983). Galanin-like peptide (GALP), called alarin, is a hypothalamic neuropeptide belonging to the galanin family of peptides (Ohtaki et al., 1999). It is argued that both GAL and GALP exert their cellular effects by activating galanin receptors (Lang et al., 2015). These receptors belong to the family of G-protein-coupled receptors and have been associated with many inhibitory effects on neurotransmission and memory through GAL_1-R, GAL_2-R, and GAL_3-R (Falkenstetter et al., 2020).

Based on this information, the study aimed to investigate the blood levels of various novel peptide molecules (such as PGC-1α, irisin, BDNF, GAL, GALP) that may be related to PD and, accordingly, to reveal the roles of these peptides in PD. Thus, it is thought to contribute to the diagnosis and treatment of the disease as well as to clarify the pathogenesis of PD.

MATERIALS and METHODS

Ethics statement

This study was conducted in accordance with the Helsinki Declaration. Prior to the study, necessary permissions were obtained from Kafkas University, Faculty of Medicine, Local Ethics Committee (Date: 27.02.2019 No: 2019-02-78).

Study design

This study, designed as a cross-sectional, was consisted of the patient group and the control group. The study was designed by a neurologist in Kafkas University Health Research and Application Hospital Neurology Department in a way that 45 newly diagnosed voluntary individuals with idiopathic Parkinson's disease within the first three stages according to the

(Hoehn and Yahr, 1967) scale and the "UK Brain Bank" diagnostic criteria (Hughes et al., 1992) would constitute the patient group of the study and 45 voluntary individuals without Parkinson's or any neurodegenerative disease would constitute the control group of the study. With regard to the inclusion criteria of all patients to be included in the study, the age range was determined as 45-90 years. For the patient group, the criteria such as the presence of a history or signs of neurological disease other than Parkinson's disease, having PD in the 4th or 5th stage according to the (Hoehn and Yahr, 1967) scale, the presence of secondary parkinsonism, Parkinson-plus syndromes, or hereditary degenerative disease, heavy exercise and fasting exceeding 24 hours, alcohol and substance abuse, the use of antioxidant preparations, and willingness to leave the study constituted the exclusion criteria of the study. The criteria such as the presence of dementia or another neurodegenerative disease, heavy exercise, fasting exceeding 24 hours, alcohol and substance abuse, the use of antioxidant preparations, and willingness to leave the study were determined as the exclusion criteria for the control group. In the study, for biochemical examinations on a voluntary basis (accepting the Informed Consent Form), 5 ml blood samples from individuals with brachial intravenous access were taken into biochemistry tubes (BD Vacutainer® tubes, BD-Plymouth. PL6 7L6, UK) containing ethylenediamide tetraacetic acid (EDTA). Tubes were gently shaken several times for Anti-coagulation. To eliminate the activity of proteinases, the collected blood samples were transferred to centrifuge tubes pre-added with aprotinin (0.6 TIU/ml of blood), (Catalog No: RK-APRO, Phoenix Pharmaceuticals, Belmont, CA, USA) and gently shaken again. The collected blood samples were centrifuged for 1,600 x g for 15 minutes at 4°C without wasting time in the Biochemistry Laboratory of Kafkas University Health Research and Application Hospital to obtain plasma. This process continued until the plasma samples became clear. The plasma samples obtained were portioned in Eppendorf tubes and kept at -80°C until the analysis of the peptides.

Biochemical analysis

PGC1-α, irisin, BDNF, GAL, and GALP levels were studied in plasma samples using human ELISA kits (catalog no: YLA1036HU, YLA1361HU, YLA0580HU, YLA1774HU and YLA4151HU-lot no; YLAZXV0475, YLA64WDV0, YL018SWEJV, YLXBNYRR41 and YLV748RF3S1, respectively, Biotech Co. Ltd., Shanghai, China) as specified in the kit procedures. The absorbances were read spectrophotometrically at 450 nm on the ELX800 ELISA Reader. Bio-Tek ELX50 (BioTek Instruments, USA) was used as an automatic washer in plate washing. The results were reported as ng/mL for PGC1-α, ng/mL for irisin, ng/mL for BDNF, ng/L for GAL, and pg/mL for GALP. The measuring ranges of the kits were 0.05 ng/mL-30 ng/mL, 0.2 ng/mL-60 ng/mL, 0.05 ng/mL-10 ng/mL, 0.5 ng/L-100 ng/L, and 3 pg/mL-380 pg/mL, respectively. The minimum measurable levels of the kits were 0.021 ng/mL, 0.095 ng/mL, 0.01 ng/mL, 0.26 ng/mL, and 1.03 pg/mL, respectively. The intra-assay and inter-assay coefficient variables (CV%) of all kits were < 10%. All ELISA analyses in this study were performed in Kafkas University Faculty of Medicine Medical Biochemistry R&D laboratory.

Statistical analysis

All data obtained from the study were analyzed using the Statistical Package for Social Science (SPSS®) Version 22.0 (SPSS Inc, Chicago, USA) for Windows® in order to reveal the differences in the disease and control groups. The Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to determine the distribution of continuous data in terms of normality. Student's t-test was applied to parametric data to reveal the mean differences of ages between the groups. The Mann-Whitney U test was applied to nonparametric data to compare the median plasma peptide levels between the groups. Spearman's correlation analysis was performed to examine the correlations between data. For numerical variables, the descriptive statistics were expressed as group mean ± standard

deviation (Mean ± S.D) or median (minimum value – maximum value). In the analysis, $p < 0.05$ was used to express the lowest level of significance.

RESULTS

Gender and age

The study consisted of a total of 90 individuals, including 45 healthy individuals (male/female 20/25) and 45 individuals with Parkinson's disease (male/female 18/27). In our study, the mean age of the Parkinson's patient group (72.1 ± 6.01 years) was not found to be statistically significantly higher compared to the mean age of the control group (69.8 ± 5.84 years) ($p = 0.059$) (Table 1).

Table 1. Comparison of the Mean Age and Plasma Peptide Levels by the Groups

	CONTROL (n=45) Mean±SD Median(min-max)	**PD (n=45) Mean±SD Median(min-max)**	***P-value***
Age (year)	69.80 ± 5.84	72.10 ± 6.01	0.059
PGC1-α (ng/mL)	5.98 (4.99-7.03)	3.38 (2.60-4.43)	0.042[a]
Irisin (ng/mL)	18.77 (15.01- 20.53)	12.77 (9.70-15.04)	0.040[a]
BDNF (ng/mL)	4.39 (3.70-4.95)	1.61 (1.35-2.01)	0.008[aa]
GAL (ng/L)	21.32 (16.70-25.87)	15.46 (12.98-17.77)	0.022[a]
GALP (pg/mL)	48.92 (28.66-69.68)	47.68 (32.5-65.86)	0.084

PD: refers to the group of patients with Parkinson's disease; **SD**: refers to standard deviation; **PGC1-α**: proliferator-activated receptor alpha; **BDNF**: brain-borne neurotrophic factor; **GAL**: galanin; **GALP**: galanin-like peptide;

p: indicates the significance in ages and plasma peptides levels between the groups according to Student's t-test and the Mann-Whitney U test;

[a]**p-value** <0.05; compared to the control group (according to the Mann-Whitney U test),

[aa]**p-value** <0.01; compared to the control group (according to the Mann-Whitney U test).

Biochemical analysis results

When plasma PGC1-α, irisin, BDNF, GAL, and GALP levels between the groups were examined, it was determined that the median levels of the patient group (3.38 [2.60-4.43] ng/mL, 12.77 [9.70-15.04] ng/mL, 1.61 [1.35-2.01] ng/mL, 15.46 [12.98-17.77] ng/L, and 47.68 [32.5-65.86] pg/mL, respectively) were lower compared to the control group (5.98 [4.99-7.03] ng/mL, 18.77 [15.01- 20.53] ng/mL, 4.39 [3.70-4.95] ng/mL, 21.32 [16.70-25.87] ng/L, and 48.92 [28.66-69.68] pg/mL, respectively) ($p = 0.042$, $p = 0.040$, $p = 0.008$, $p = 0.022$, and $p = 0.084$, respectively) (Table 1). According to Spearman's correlation analysis performed to reveal the correlation between the selected peptides in order to shed light on the pathogenesis of the disease, significant positive low correlations were found between plasma BDNF levels and irisin and galanin ($r = 0.271$; $p = 0.011$, $r = 0.348$; $p = 0.001$, respectively). Significant positive moderate correlations were found between plasma PGC1-α levels and BDNF, irisin and GAL ($r = 0.685$, $r = 0.424$ and $r = 0.532$, respectively, $p \leq 0.001$ for all p-values). Furthermore, negative correlations were found between age and plasma peptide levels. Here, only the correlation in plasma BDNF levels was found to be statistically significant ($p = 0.040$; $r = -0.225$) (Table 2).

DISCUSSION

Parkinson's disease has been associated with aging, and dopaminergic neurons in the substantia nigra, which play a role in its pathogenesis, decrease by 4.7%-9.8% in every decade with aging (Akbayır et al., 2017). When the literature is reviewed, it is reported that the disease typically occurs in individuals aged 60 and over and that its incidence is higher in men (Kalia and Lang, 2015). Our study was compatible with the literature in terms of the mean age of the patient group (Table 1) and the

incidence by gender. Also, in the study, it was determined that there was no statistically significant difference between the mean age of the PD diagnosed and the control group. These findings show that the ages of the two groups that make up our study are close to each other and homogeneously distributed.

Mitochondrial dysfunction play an important role in the formation and progression of neurodegeneration in PD and oxidative stress caused by free radicals in the endoplasmic reticulum and nucleus membrane (Pieczenik and Neustadt, 2007; Cao and Kaufman, 2014; Siuda et al., 2017). In Parkinson's disease, PGC1-α is downregulated, and consequently, genes that control cellular bioenergetics and mitochondrial biogenesis regulated by PGC1-α are expressed insufficiently (Eschbach et al., 2015). In our study, PGC1-α levels were statistically decreased in the patient group compared to the control group (Table 1). Decreased PGC1-α function may have caused mitochondrial dysfunction and death of neurons in an inflammatory environment associated with excessive oxidative stress. Indeed, some studies support the our finding (Su et al., 2015; Yang et al., 2018).

Table 2. Correlations Between the Parameters Examined

		Age	BDNF	Irisin	GAL	GALP	PGC1- α
Age	Spearman's Correlation	1	-.225*	-.007	-.047	-.061	-.072
	Sig. (2-tailed)		.040	.950	.663	.570	505
BDNF	Spearman's Correlation	1	.271*	.348*	.084	.685**	
	Sig. (2-tailed)		.011	.001	.153	.000	
Irisin	Spearman's Correlation	1	.567**	.104	.424**		
	Sig. (2-tailed)		.000	.132	.000		
GAL	Spearman's Correlation	1	.154	.532**			
	Sig. (2-tailed)		.087	.000			
GALP	Spearman's Correlation	1	.080				
	Sig. (2-tailed)		.162				
PGC1- α	Spearman's Correlation	1					
	Sig. (2-tailed)						

BDNF: Brain-derived neurotrophic factor; **GAL:** Galanin; **GALP:** Galanin-like peptide; **PGC1-α:** Peroxisome proliferator-activated receptor gamma coactivator *1-alpha;*

According to Spearman's correlation analysis:

***Correlation is significant at the 0.05 level (2-tailed),

****Correlation is significant at the 0.01 level (2-tailed).

As far as we know, there is no study evaluating plasma irisin levels of Parkinson's patients in the literature. Studies on obesity, glucose homeostasis, and exercise constitute most of the studies on irisin, which has been discovered as a new myokine in recent years (Moreno et al., 2013; Choi et al., 2013; de Oliveira Bristot et al., 2019). Among the therapeutic potentials of irisin, researchers demonstrated that it played a role in the regulation of metabolism and the suppression of oxidative stress, anti-inflammatory and neuroprotective effects, and it was reported that PGC1-α had an effect on irisin to fulfill these roles (Rabiee et al., 2020). It is suggested that this effect of PGC1-α is mediated by Fibronectin type III domain-containing protein 5 (FNDC5), a type-1 membrane protein that is a precursor to irisin. A study, It was reported that increased expressions of PGC1-α as a result of physical activity and cold exposure led to increases in FNDC5, and proteolysis of FNDC5 protein in an unknown way leads to the production of irisin. (Zarbakhsh et al., 2019). In our study evaluating the level of irisin in Parkinson's patients, the level of irisin was found to be statistically significantly lower in the patient group compared to the control group (Table 1). Accompanied by the above mechanisms, In the study, plasma lower levels of irisin in patients with Parkinson's disease may

be due to low PGC1-α levels, and it can be interpreted that the decrease in PGC1-α decreased the level of irisin by decreasing the breakdown of irisin. This mechanism was also supported by the correlation (Table 2).

It is known that the BDNF protects dopaminergic neurons and improves dopaminergic neurotransmission and motor performance (Palasz et al., 2020; Zhang et al., 2020). In a study, it was found that blood BDNF levels were significantly lower in Parkinson's patients compared to patients with ET (essential tremor) and controls (Huang et al., 2019). In a similar recent study, it was reported that BDNF levels were found to be lower in the Parkinson's patient group compared to the healthy group and that there was a significant correlation between low BDNF levels and cognitive disorders (Ng et al., 2019). The results of our study are consistent with the literature in that it was observed that plasma BDNF levels decreased in Parkinson's patients compared to healthy controls in our study (Table 1). These results indicate that low BDNF level plays an important role in the pathophysiology of PD. In our study, the fact that a significant positive correlation was found in the correlation between BDNF and irisin levels suggested that low BDNF level in PD might be caused by the low level of irisin (**Table 2**) because various studies showed that irisin promoted STAT-3 signal activation and BDNF release in improving cognitive function and the consequences of neurodegenerative diseases (Jin et al., 2018; Siuda et al., 2017; Wrann, 2015). Furthermore, the decrease in BDNF levels in the patient group may have been caused by the decrease in sirtuin-1 (SIRT-1) due to aging, in addition to the decrease in irisin levels because it was reported that SIRT-1 levels decreased with aging in neurons in the brain, resulting in a decrease in BDNF levels, which is an important neurotrophic factor regulating learned memory and synaptic function (Lee et al., 2019). In our study, a significant negative correlation was found in the correlation between age and BDNF (Table 2). Although it seems to support the mechanism mentioned above, the fact that SIRT-1 levels could not be examined in our study indicates a limitation of our study, which prevents making a clear comment on this issue. We would like to indicate that more detailed studies are needed on this issue. Galanin shows its cellular activities through its receptors (GalR-1, GalR-2, and GalR-3) (Lang et al., 2005). These receptors are involved in signal transduction by multiple signal transduction pathways in the neuronal cell, including the inhibition of cyclic AMP/protein kinase A (by GalR-1, GalR-3) and the stimulation of phospholipase C (by GalR-2) (Lang et al., 2007). Galanin modulates the neurotransmitter system with the cholinergic, noradrenergic, serotonergic, and neuroendocrine pathways in the mammalian central nervous system (CNS) (Counts et al., 2010). GAL, which is also a neuropeptide, plays an important role in energy metabolism and sleep homeostasis, food intake, cognitive functions and behaviors in vertebrates (Shioda et al., 2011). As far as we know, there is no study examining the plasma levels of GAL and GALP in PD in the literature. In our study, while GAL levels were statistically decreased in the Parkinson patients group compared to the control group, the decrease in GALP levels was found to be statistically insignificant (Table 1). Although it was reported in the literature that GAL levels increased in neurodegenerative diseases due to the cholinergic system (by suppressing the cholinergic system), GAL levels were interestingly found to be low in Parkinson's patients in our study, which is inconsistent with the literature. Furthermore, this low value was supported by the positive correlation between PGC1-α and BDNF and GAL (Table 2). These results suggested that GAL had its effect through PGC1-α and BDNF in promoting neuroprotection and neuroplasticity in patients with Parkinson's disease. The fact that the decreases in plasma GALP levels in Parkinson's patients were not correlated with the decreases in GAL, BDNF, PGC1-α levels was interpreted that two peptides belonging to the same family did not function with the same mechanisms in Parkinson's patients. These results should be supported by

more detailed studies on the diagnosis and treatment of PD in the future.

Based on this information, plasma levels of irisin, PGC1-α, BDNF, GAL, and GALP in PD were found to be low. We believe that these peptides, which we have studied, will shed light on more detailed studies to be conducted in the future to shed light on their roles in the pathophysiology of PD.

Disclosure Statement

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by Kafkas University Scientific Research Projects Coordination Office (KAUBAP), [grant number: 2019-TS-62]. We thank KAUBAP for their support.

Author Contribution Statement

Concept, Design and Supervision- HFG; Data collection and interpretation- HFG, CEE; Data analysis- HFG, CY; Literature search- HFG, CY, OG, IA; Writing- HFG; Critical review- HFG, CY, CEE, OG, IA

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