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The clinical and immunological characteristics of common variable immunodeficiency in adults and older adults

Eray Yildiz,[1] Fatih Colkesen,[2] Recep Evcen,[2] Filiz Sadi Aykan,[2] Mehmet Kilinc,[2] Gokhan Aytekin,[3] Sevket Arslan[2]

[1]Department of Clinical Immunology and Allergy, Necip Fazil City Hospital, Kahramanmaras, Turkiye

[2]Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkiye

[3]Department of Clinical Immunology and Allergy, Konya City Hospital, Konya, Turkiye

ABSTRACT

OBJECTIVE: The aim of this study was to determine the clinical and immunological characteristics of older adults with common variable immunodeficiency (CVID).

METHODS: Patients aged ≥18 years who were followed up with the diagnosis of CVID between 2015 and 2020 were included in the study. The patients were separated into two age groups according to the age at diagnosis: the adult group, aged 18-65 years (n=49) and the older adult group, aged ≥65 years (n=11).

RESULTS: Splenomegaly (55.1% vs. 9.1%, p=0.006), bronchiectasis (53.0% vs. 9.1%, p=0.008), and autoimmunity (42.8% vs. 9.1%, p=0.036) were determined to be more common in the adult group than in the older adults. A similar frequency of malignancy was seen in both groups (6.1% vs. 9.1%, p=0.721). There were significantly more patients with no comorbidity in the older adult group than in the adult group (45.5% vs. 16.3%, p=0.034). Serum IgG and IgA levels were determined to be significantly higher in the older adult group than in the adult group (p=0.001 for all). The $CD19^+$ B-cell count at the time of diagnosis was determined to be lower and the $CD19^+CD27^+IgD^-$ switched memory B-cells and $CD16^+CD56^+$ natural killer cell counts were higher in the older adults than in the adult group (p=0.016, p=0.032, p=0.044, respectively).

CONCLUSION: Knowledge of clinical and immunological differences in older adult CVID patients may be of benefit in polyclinic follow-up and in respect of changes to be made to the treatment plan.

Keywords: Common variable immunodeficiency; clinical phenotype; immunosenescence; older adults.

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Common variable immunodeficiency (CVID) is an inborn error of immunity (IEI) (formerly defined as primary immunodeficiency [PID]) characterized by hypogammaglobulinemia [1–3]. CVID is the most frequently seen symptomatic immunodeficiency in adults [4]. It is seen with heterogeneous complications and comorbidities, such as recurrent bacterial infections, lymphoproliferation, autoimmune disorders, chronic lung disease, gastrointestinal diseases, and increased risk of malignancy [5].

CVID is generally diagnosed after adolescence, with most patients diagnosed between the ages of 25 and 45 years [6, 7]. The records of the European Society for Im-

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Correspondence: Eray YILDIZ, MD. Necip Fazil Sehir Hastanesi, Klinik Immunoloji ve Alerji Klinigi, Kahramanmaras, Turkiye.
Tel: +90 344 228 23 47 e-mail: drerayyldz@gmail.com

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munodeficiency (ESID) state that PID patients over the age of 65 constitute 8% of all PID patients and CVID has been determined to be the most commonly seen PID in this age group [8]. However, very little is known about the clinical characteristics of older adult CVID patients [9]. The aim of this study was to determine the immunological findings and clinical characteristics of older adult CVID patients and to examine the similarities and differences with adult patients.

MATERIALS AND METHODS

Study Design

The study included patients aged ≥18 years who were diagnosed with CVID and were followed up in the immunology unit of our clinic between January 2015 and June 2020. The patients were separated into two age groups according to the age at diagnosis: the adult group, aged 18-65 years (n=49) and the older adult group, aged ≥65 years (n=11) [10]. All the patients met the ESID updated diagnostic criteria for CVID [4]. Patients aged <18 years or with secondary causes of hypogammaglobulinemia (eg., drugs [corticosteroids, anti-epileptic drugs], malignancies, infections, protein-losing enteropathy) were excluded from the study.

Ethics Approval

This study protocol was reviewed and approved by Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee (date: 03.07.2020 and 19.11.2021, number: 2020/2660 and 2021/3494). The study was conducted according to the Declaration of Helsinki. This retrospective review of patient data did not require written informed consent from participants in accordance with local guidelines.

Data Collection

The demographic, clinical, and laboratory data of all the study participants were retrieved from the medical records. The information of age, gender, medical history, serum Ig levels, total lymphocyte count, flow cytometry of peripheral blood lymphocyte subgroups, serum albumin and/or stool alpha-1 Antitrypsin levels, respiratory function tests, imaging methods (ultrasonography, computed tomography [CT], endoscopy, colonoscopy), and pathology evaluation results were obtained from the electronic medical records and the archived patient files in the immunology unit.

Highlight key points

- Higher serum IgG levels make early diagnosis of CVID difficult in older adults.
- Comorbid conditions facilitate early detection of CVID.
- Comorbid conditions in older adults are associated with peripheral lymphocyte subsets.

Clinical Characteristics

The CVID patients were separated in 4 groups according to similar clinical and phenotype characteristics; lymphoproliferation, autoimmunity, gastrointestinal (GI)/liver disease, and malignancy. Current or previous lymphadenopathy and/or hepatomegaly and/or splenomegaly, granulomatous and lymphocytic interstitial lung disease were accepted as lymphoproliferation.

Autoimmune hemolytic anemia, immune thrombocytopenia, Evans syndrome, neutropenia, autoimmune hepatitis, thyroiditis, Sjögren's syndrome, systemic lupus erythematosus, and type 1 diabetes mellitus were accepted as autoimmunity. Inflammatory bowel disease, malabsorption, cirrhosis of unknown etiology and chronic hepatitis of unknown origin were accepted as GI/liver disease. Cancer types associated with CVID (lymphoid, GI adenocarcinoma) and non- (eg, sarcomas, glioblastomas) have been defined as malignancies. Bronchiectasis was proven with CT but as there was no objective evidence, it was not included in the phenotyping and was defined separately.

Immunological Characteristics

Serum Ig measurement; serum Ig levels (IgG, IgA and IgM) were determined using nephelometric methods (Siemens BNII System, Erlangen, Germany).

For the immunophenotyping by flow cytometry; complete blood counts were performed with Sheath reagent using the Abbott Cell Dyn 3700 series (USA). Peripheral blood lymphocyte subsets were measured with a BD FACSCanto II 8-color flow cytometer system (Erembodegem, Belgium) with fluorescence-labeled antibodies. Measurements were taken of $CD3^+$ T-cells, $CD4^+$ T-cells, $CD8^+$ T-cells, $CD19^+$ B-cells, $CD19^+CD27^+IgD^-$ switched memory B (SMB)-cells, and $CD16^+CD56^+$ natural killer (NK) cells [11].

Specific antibody responses; pneumococcal polysaccharide antibody titers were measured using a multiplexed immunoassay (Elizen, Angleur, Belgium). An impaired response to the Pneumovax-23 vaccine was considered if the post-vaccination titer was <1000 mU/

Table 1. Clinical characteristics of the patients with common variable immunodeficiency

Clinical characteristics	Adults (18–65 years) (n=49)	Older adults (≥65 years) (n=11)	p*
Age, years, means±SD	38.1±12.4	75.8±7.4	
Symptom onset age, years, means±SD	23.9±17.1	71.8±7.6	
Age at diagnosis, years, means±SD	30.5±15.7	73.5±7.4	
Duration of illness, months, means±SD	89.4±79.7	27.4±18.3	**0.014**
Delay in diagnosis, months, means±SD	78.8±78.9	39.1±28.9	0.108
Sex, %			
Female	44.9	36.3	0.606**
Male	55.1	63.6	0.606**
Mortality, %			
All cause	14.3	45.5	**0.020****
CVID-related	10.2	36.4	**0.028****

*: Independent samples t-test (data were shown as mean with standart deviation); **: Chi Square test (data were shown as number and percentages); SD: Standard deviation; CVID: Common variable immunodeficiency.

mL or a less than-twofold increase over the pre-vaccination titer. Tetanus antitoxin IG ELISA (Novalisa, Vienna, Austria) kits were used to detect tetanus antibodies. Tetanus antitoxin IgG was accepted as an antibody at a protective level ≥0.1 IU/mL. To measure the isohemagglutinin titer, blood samples in EDTA tubes were centrifuged at 5000 rpm for 1 min. After centrifugation, the separated plasma was diluted with physiological saline for titration. Titers ≥1:8 were considered normal.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows v.22.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables as number (n) and percentage (%), and continuous variables were stated as mean±standard deviation (SD) or median (min-max) values. For the comparison of categorical variables, the Pearson Chi-square test was applied. In the comparisons of independent groups of continuous variables, the Mann Whitney U-test (non-parametric) or the Independent Samples t-test (parametric) were used. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Patient Population

Evaluation was made of a total of 60 CVID patients, 11 in the older adult group and 49 in the adult group. In the adult group, the mean age of the patients was 38.1±12.4 years and the mean age at diagnosis was 30.5±15.7 years.

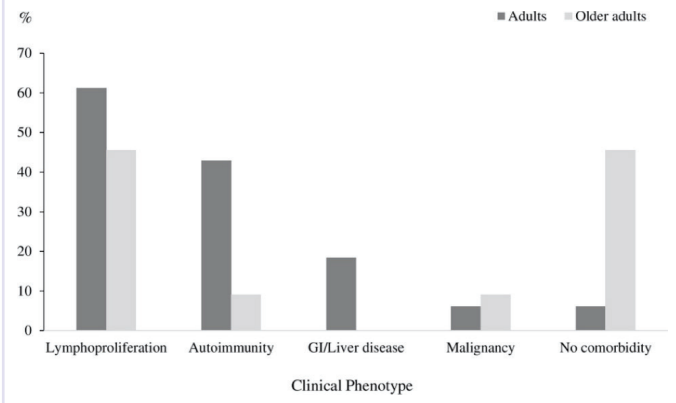

Figure 1. The distribution of clinical phenotypes in adult and older adult CVID patients.

CVID: Common variable immunodeficiency; GI: Gastrointestinal.

In the older adult group, the mean age was 75.8±7.4 years and the mean age at diagnosis was 73.5±7.4 years. The duration of disease was determined to be shorter in the older adult group than in the adult group (p=0.014). The mortality rate of the entire patient group was found to be 20% (n=12). Both all-cause and CVID-related mortality were found to be higher in the older adult group compared to the adult group (respectively, p=0.020, p=0.028) (Table 1).

Clinical Characteristics

The most frequently seen clinical phenotype in both the adult and older adult groups was found to be lymphoproliferation (61.2%, 45.5%, respectively) (Fig. 1, Table 2).

Table 2. Clinical features of adults and older adults with common variable immunodeficiency

	Adults (18–65 years) (%)	Older adults (≥65 years) (%)	p*
Total (n=60)	82	18	
Lymphoproliferation	61.2	45.5	0.338
Splenomegaly	55.1	9.1	**0.006**
Lymphadenopathy	24.5	18.2	0.655
Hepatomegaly	6.1	18.2	0.191
GLILD	2.0	0	–
Autoimmunity	42.9	9.1	**0.036**
ITP	14.3	0	–
AIHA	14.3	0	–
Neutropenia	8.2	0	–
Evans syndrome	4.1	0	–
AIH	4.1	0	–
Thyroiditis	4.1	9.1	0.491
Sjögren's syndrome	4.1	0	–
Type 1 DM	2.0	0	–
SLE	2.0	0	–
GI/Liver disease	18.4	0	–
Inflammatory bowel disease	6.1	0	–
Malabsorption	2.0	0	–
Cirrhosis of unknown etiology	6.1	0	–
Chronic hepatitis of unknown origin	4.1	0	–
Malignancy	6.1	9.1	0.721
CVID-associated lymphoid malignancies	6.1	9.1	0.721
No comorbidity	16.3	45.5	**0.034**
Bronchiectasis	53.1	9.1	**0.008**

GLILD: Granulomatous and lymphocytic interstitial lung disease; ITP: Immune thrombocytopenia; AIHA: Autoimmune hemolytic anemia; AIH: Autoimmune hepatitis; DM: Diabetes mellitus; SLE: Systemic lupus erythematosus; DHR: Drug hypersensitivity reactions; GI: Gastrointestinal; CVID: Common variable immunodeficiency; *: Chi Square test (data were shown as number and percentages).

Splenomegaly (55.1% vs. 9.1%, p=0.003), bronchiectasis (53.1% vs. 9.1%, p=0.008), and autoimmunity (42.9% vs. 9.1%, p=0.036) were determined to be more common in the adult group than in the older adults. A similar frequency of malignancy was seen in both groups (6.1% vs. 9.1%, p=0.721). There were significantly more patients with no comorbidity in the older adult group than in the adult group (45.5% vs. 16.3%, p=0.034) (Table 2).

A patient may have more than one phenotype. Therefore, there may be overlaps between clinical phenotypes (Fig. 2).

Immunological characteristics

Serum IgG and IgA levels at the time of diagnosis were determined to be significantly higher in the older adult group than in the adult group (p=0.001 for all). The $CD19^+$ B-cell count at the time of diagnosis was determined to be lower and the SMB-cell and NK-cell counts were higher in the older adults than in the adult group (p=0.016, p=0.032, p=0.044, respectively) (Table 3).

Relationships Between Clinical Phenotypes and Immunological Characteristics

The patients with lymphoproliferation comprised 30 adults and 5 older adults. The serum IgG and IgA levels were determined to be higher in the older adults than in the adults with lymphoproliferation (p=0.029, p=0.004, respectively), and the $CD19^+$ B-cell counts were lower (p=0.010) (Fig. 3).

DISCUSSION

IEI are inherited defects of the immune system and are considered primary because the disease process originates in the immune system itself. Information on immunodeficiencies in older adults was limited to the more common secondary forms of disease [8, 12]. However, together with the developments in diagnosis and clinical management, IEI has become more important in older adults. Data obtained from the ESID records has shown that the vast majority (89.4%) of older adults suffer from antibody deficiency syndromes and the majority (63.3%) of those consist of CVID [8]. However, there is insufficient data in this field. The diagnostic and treatment approaches for this patient group are based on the clinical experience obtained from a younger patient group.

Categorization of CVID into clinical phenotypes has been shown to be important in the determination of prognosis. Moreover, immunological abnormalities seen in CVID patients have been associated with clinical phenotypes of the disease [13–15]. Due to the heterogeneous nature of CVID, the patients in the current study were separated into subgroups of similar clinical and phenotypic characteristics (lymphoproliferation, autoimmunity, GI/liver disease, malignancy). The only previous study in this area is the study by Fortier et al. [9], in which CVID patients aged >40 years were evaluated, whereas in the current study, evaluations were made of older adult patients aged ≥65 years. Consistent with the previous study, the incidence of splenomegaly and autoimmunity was found to be lower in the older adults of the current study population.

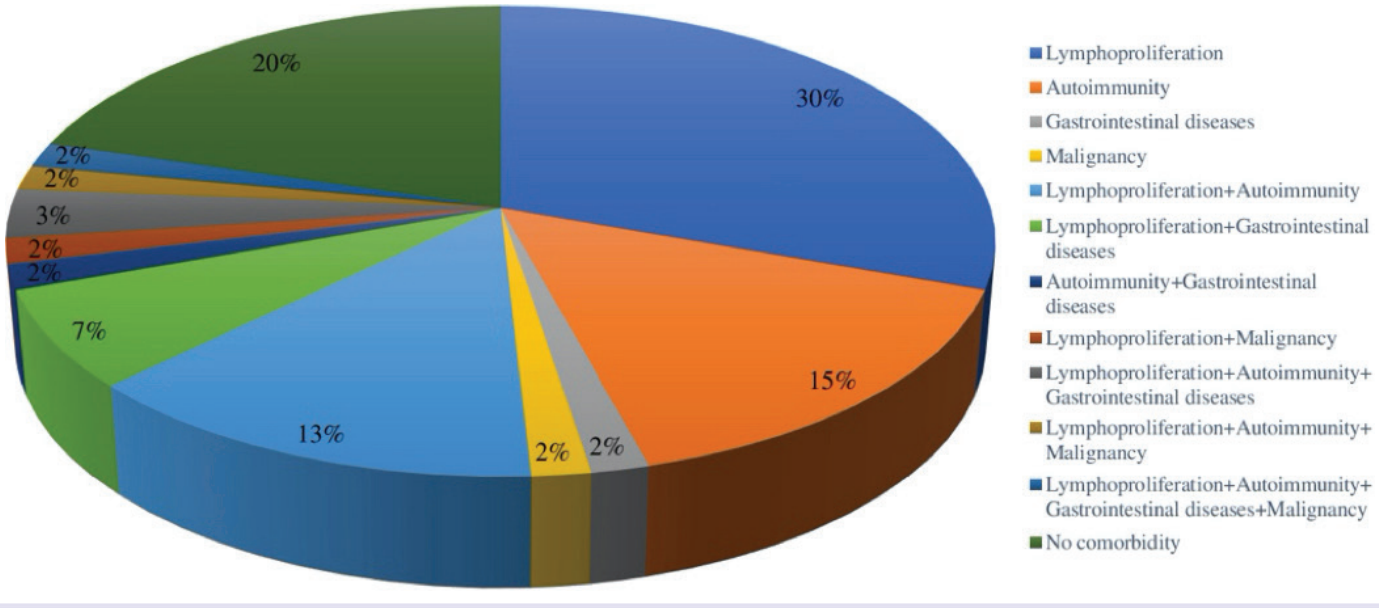

FIGURE 2. Frequency and overlap of clinical phenotypes in patients with CVID (n=60). CVID, common variable immunodeficiency.
*Evaluation was done in all CVID patients.

TABLE 3. Immunological characteristics of adult and older adult common variable immunodeficiency patients

	Reference range	Adults (18–65 years) n=49	Older adults (≥65 years) n=11	p*
IgG (mg/dL)	700–1600	278 (33–593)	530 (278–570)	**0.001**
IgA (mg/dL)	70–400	25 (0–359)	62 (33–190)	**0.001**
IgM (mg/dL)	40–230	26 (9–217)	31 (17–94)	0.534
Total lymphocyte (cell/μL)	1000–4800	1330 (250–3910)	1200 (130–5300)	0.626
$CD3^+$ T cells (cell/μL)	998–5625	1117.2 (192.5–3558.1)	904.8 (44.8–4240)	0.695
$CD4^+$ T cells (cell/μL)	673–3110	424.0 (5.0–1500.0)	408.1 (20.1–2067.0)	0.782
$CD8^+$ T cells (cell/μL)	238–1570	570.0 (115.5–2756.6)	436.8 (22.8–1643.0)	0.738
$CD19^+$ B cells (cell/μL)	87–541	73.8 (0–540.0)	30.8 (0–86.8)	**0.016**
$CD19^+CD27^+IgD^-$ SMB cells (cell/μL)	10–171	0.6 (0–32.3)	4.2 (0–13.9)	**0.032**
$CD16^+$ $CD56^+$ NK cells (cell/μL)	91–766	72.0 (0–242.0)	162.4 (36.9–742)	**0.044**

Ig: Immunoglobulin; SMB: Switched memory B; NK: Natural killer; *: Mann-Whitney U test (data were shown as median with min–max).

The incidence of bronchiectasis was determined to be similar in the different age groups in the Fortier study [9], but in the current study it was found to be lower in older adults. Malignancy was observed at an equal frequency in the two age groups of the current study, and the absence of disease-related comorbidity was more common in older adults. Separation of CVID into subgroups can be helpful for a better understanding of the heterogeneity of the disease. The lower incidence of comorbidities such as splenomegaly, bronchiectasis and autoimmunity in older adults can make CVID diagnosis more difficult. The fact that adults have symptoms for an average of 7.5 years but older adults for only 2 years may explain why the incidence of comorbidity is significantly lower in the older cohort. However, the high incidence of both all-cause and CVID-related mortality in older adults and the incidence of malignancy equal to that in adults indicate that the course of the disease is not slow. However, the fact that there was no significant difference in the delay in diagnosis between the groups, implies that CVID developed later in the older age group.

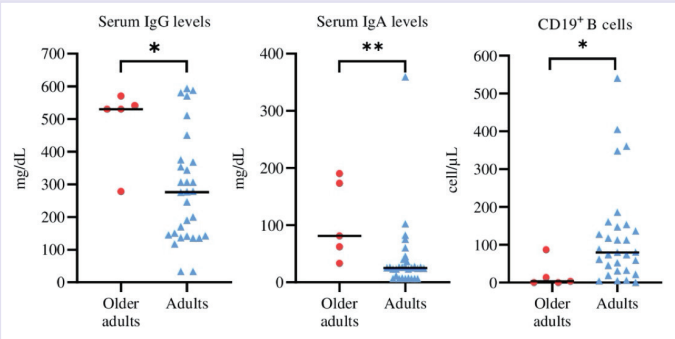

Figure 3. The serum IgG and IgA levels, and CD19+ B-cell counts in the adult and older adult CVID patients with lymphoproliferation.

CVID: Common variable immunodeficiency; *: P<0.05; **: P<0.01.

Various studies have reported B and T-cell abnormalities in adult CVID patients, and these have been associated with clinical phenotypes of the disease [16–18]. Although there are several studies that have compared the clinical and immunological characteristics of CVID patients with pediatric or adult onset [19, 20], there are insufficient studies that have evaluated the characteristics of older adult CVID patients. In this study, compared to the adult patients, the older adults were determined to have higher serum IgG and IgA levels, higher SMB and NK-cell counts and lower $CD19^+$ B-cell counts. Older adults have higher serum IgG levels at the time of diagnosis, making it difficult to diagnose CVID early.

Ageing is a complex process in which many changes occur in the physiological systems of the body. One of the most important changes together with ageing occurs in the immune system and this is known as immunosenescence [21]. Although T-cell changes have been mainly focused on, both B-cell and T-cell compartments are affected by ageing [22]. An increase in IgG and IgA levels and a decrease in IgM levels occur together with ageing [23], and there has been shown to be a significant decrease in $CD19^+$ B-cell count [24, 25]. It is also thought that the increase in SMB-cell counts could be a differentiating characteristic of B-cell immune ageing [26]. An increase in NK-cell count has also been determined together with ageing [27]. Although CVID is an IEI, the changes occurring in the immune system of older adult CVID patients cannot be explained by congenital defects alone. The results obtained in the current study suggest that immunosenescence could have an effect on the changes occurring in older adult CVID patients.

Lymphoproliferation is a common characteristic of CVID and has been associated with a decrease in $CD19^+$ B-cell count [28]. Lymphoproliferation was determined in 58.3% of the CVID patients in the current study, and of these, 14.3% were in the older adult age group. Compared to the adult group, lymphoproliferation in older adults was associated with higher serum IgG and IgA levels and lower $CD19^+$ B-cell counts.

In this study, the clinical and immunological characteristics of older adult CVID patients were evaluated, and the similarities and differences were compared with adult CVID patients. Thus, the most important limitation of the study is the low number of older adult CVID patients. Nevertheless, the data obtained in this study can be considered a reference for further studies with larger cohorts.

Conclusion

The results of this study determined various clinical and immunological abnormalities in older adult CVID patients that were different from adult age group patients. It appears that the key observations here are that having older adults with higher IG levels makes it less likely that CVID will be diagnosed early and that having a comorbid condition increases the likelihood of earlier diagnosis. The fact that there was no significant difference in the delay between onset of symptoms and diagnosis between the groups, implies that CVID developed later in the older age group.

In addition, the abnormalities seen in serum Ig levels and the peripheral lymphocyte subgroups were related to organ involvement. Knowledge of these clinical and immunological differences in older adult CVID patients may be of benefit in polyclinic follow-up and in respect of changes to be made to the treatment plan. Nevertheless, there is a need for further studies of larger populations to confirm these results.

Ethics Committee Approval: The Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee granted approval for this study (date: 03.07.2020 and 19.11.2021, number: 2020/2660 and 2021/3494).

Authorship Contributions: Concept – EY, SA, FC; Design – EY, FA, SA; Supervision – EY, RE, FSA; Materials – RE, MK, GA; Data collection and/or processing – FSA, MK, GA; Analysis and/or interpretation – FSA, GA; Literature review – RE, MK; Writing – EY, FC; Critical review – EY, SA.

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