Journal of Clinical Immunology
https://doi.org/10.1007/s10875-019-00666-9

ORIGINAL ARTICLE

How to Identify Common Variable Immunodeficiency Patients Earlier: General Practice Patterns

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Received: 23 April 2019 / Accepted: 8 July 2019
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Abstract

Purpose Diagnostic delay is a major problem concerning common variable immunodeficiency (CVID). We aimed to determine the pattern of general practitioner (GP) consultations in individuals diagnosed with CVID within 3 years before the diagnosis and whether the risk of diagnosis was associated with the frequency of consultations or character of examinations.

Methods We conducted a nested case-control study, identifying 132 adult CVID patients and 5940 age- and gender-matched controls from national registers during 1997–2013. We used conditional logistic regression to calculate the odds ratios (OR) and 95% confidence intervals (95%CI).

Results The median number of consultations among individuals with CVID was more than twice that of the controls in all 3 years (3rd, 10; 2nd, 11.5; and 1st, 15.4 vs. 4). We found a statistically significant association between the number of consultations and the risk of a subsequent CVID diagnosis, independent of age and gender, but strongest in the individuals < 40 years. In the 3rd year before diagnosis, having 9–15 consultations compared with 1–4 was associated with an OR (95%CI) of 5.0 (2.3–10.9), 2.4 (1.1–5.4), and 1.3 (0.3–5.3) for those aged 18–40, 41–60, and > 60, respectively. Several examinations (i.e., blood tests for inflammation/infection and pulmonary function test) were associated with increased odds of a subsequent CVID diagnosis.

Conclusion The risk of a CVID diagnosis was highly related to both the number of consultations and the character of examinations performed by the GP. CVID should be a differential diagnosis among patients with multiple consultations, especially in patients < 40 years old.

Keywords CVID · PID · primary health care · consultations · diagnostic delay · indicators

Introduction

With a prevalence of approximately 1:25,000 in Europe, common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency disorder (PID) among adults in Europe [1–3]. CVID is a heterogeneous group of primary B cell defects, characterized by hypogammaglobulinemia and poor vaccine response, of

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-019-00666-9) contains supplementary material, which is available to authorized users.

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Published online: 01 August 2019

which the etiology often remains unknown [4–6]. The clinical picture of CVID is broad. The majority of CVID patients have increased susceptibility to mainly sinopulmonary infections; furthermore, autoimmune and granulomatous diseases, as well as unexplained polyclonal lymphoproliferation and certain cancers, are common [3, 7, 8].

Several studies have shown a substantial diagnostic delay (4–9 years) from the symptom onset to CVID diagnosis [1, 7, 9–11]. A recent Danish cohort study of CVID patients [3] reported a median diagnostic delay of 7 years (IQR, 3–17). The delay in diagnosis might be the result of several factors. First, the general practitioners (GPs) may have little knowledge of this relatively rare disease. Second, the heterogenic phenotype of CVID makes pattern recognition difficult. Third, the diagnosis is not made by a simple test (positive/negative) but relies on clinical criteria as well as results of more tests (i.e., hypogammaglobuline mia and poor vaccine response or a reduced number of switched memory B cells) [3, 7, 12]. And fourth, the symptoms are often progressing with time. Efforts to reduce the diagnostic delay are crucial as a late diagnosis correlates with higher morbidity and mortality, reduced quality of life, and increased health care costs compared with early and appropriate diagnosis and management [10, 13–17].

We hypothesized that CVID patients have more contacts to GPs in the years before their CVID diagnosis, compared with the general population.

We aimed to assess the fraction of CVID-diagnosed patients, who contacted their GP in the 3 years before the CVID diagnosis was established, and to investigate whether the risk of the diagnosis was associated with the frequency of consultations or character of additional examinations

Methods

Setting

As of the fourth quarter of 2018, the Danish population was approximately 5.8 million with an estimated CVID prevalence of 1:26,000 among adults [3, 18]. The Danish health care system is a universal tax-funded service, and all Danish residents have free access to primary and secondary health care. The GP carries out initial consultations and examinations and serves as a gatekeeper to the more specialized part of the health care system [19].

Design

The study design was a matched, nationwide, population-based nested case-control study.

Data Sources

All Danish citizens are given a unique 10-digit personal identification number at birth or upon immigration. The number allowed us to link the following registers on an individual level. All the registers are described in detail elsewhere [3, 20–23]. In brief, the Danish Adult Common Variable Immunodeficiency Cohort (DACC) is a historical cohort study designed to identify and characterize Danish CVID patients older than 15 years from January 1994 through December 2013 [3].

The Danish Civil Registration System (DCRS) maintains information on migration, vital status, and personal information such as civil status, date, and place of birth. DCRS is updated daily [20].

The Danish National Health Service Register (DNHSR) records data on all primary health care providers, as well as services and laboratory tests provided and reimbursed by the Danish health authorities [21].

The Danish National Patient Register, established in 1977, records data on all patients discharged from non-psychiatric hospitals and since 1995 data on all visits in outpatient departments and emergency clinics in Denmark. Diagnoses are coded by the attending physician according to the International Classification of Diseases (ICD) (8th revision (ICD-8) until December 31, 1993, and 10th revision (ICD-10) thereafter) [22].

Data on information on socioeconomic status were obtained via Statistics Denmark [23].

Participants

Cases were defined as CVID patients identified via DACC and were excluded from our study if they (1) had a missing date of CVID diagnosis, (2) were younger than 18 years at the time of diagnosis, (3) were diagnosed before January 1, 1997, and (4) had not been living in Denmark in the 3 years before diagnosis. For each case, 45 age- and gender-matched population controls were selected from the DCRS. The controls had to be alive, living in Denmark in the study period, and not diagnosed with CVID before baseline. Baseline was the date of CVID diagnosis for the matched case.

Exposure

In the 3 years before diagnosis, we assessed the following exposures:

(1) The total and annual number of GP consultations, treated as categorical variables based on different cut-offs (0, 1–4, 5–8, 9–15, and > 15 vs. 1–4) and as binary variables (≥ 5, ≥ 10, ≥ 15, and ≥ 30 consultations vs. ≤ 4), respectively. Whereas the categorical exposure variable

illustrates the results at the end of the year, the binary exposure variable was used as an attempt to illustrate the risk continuously during the year. The GP consultations were defined as all types of daytime, out-of-hours, and face-to-face consultations, as well as telephone consultation. E-mail consultations were excluded, as it was first included in DNHSR in 2003 [21].

(2) The performance of specific medical examinations (yes/no). These examinations were chosen based on clinical knowledge (~those perceived to have a clinical association with CVID or as part of the diagnostic workup of fever or suspected infections) and had a prevalence of ≥ 1% in the control group: analysis for urinary tract infections, blood testing, rapid antigen detection test for group A streptococci used to diagnose bacterial pharyngitis, blood tests for inflammation or infectious markers, measurement of hemoglobin, pulmonary function test, and analysis of biological samples excluding blood.

Statistical Analysis

Pearson's chi-squared test was used to compare baseline characteristics. A two-tailed P value ≤ 0.05 was considered statistically significant. To identify exposures associated with the risk of subsequent CVID diagnosis, we used conditional logistic regression analysis to compare exposure to different numbers of consultations and medical examinations providing odds ratios (ORs) and 95% confidence intervals (95%CI). The reference group was chosen based on the median of consultations in the control group, thus proving a more representative picture of the association between the patient and the general population. We further stratified the study population based on age, gender, and calendar year of diagnosis, to illustrate if the risk of a subsequent CVID diagnosis differed in these groups.

We performed several sensitivity analyses in which we (1) excluded individuals with very high numbers of consultations per year (> 50 per year), (2) included e-mail consultations, (3) excluded cases (and matched controls) with non-infectious onset symptoms ($n = 23$), and (4) removed patients (and matched controls) older than 60 years ($n = 28$).

The Charlson Comorbidity Index, as defined in 1987, was calculated from ICD-8 and ICD-10, during our study period from 1977 till CVID diagnosis [24].

Finally, based on the assumption that we could screen all exposed individuals for CVID, we used the fraction of exposed controls and cases in the study to estimate (1) the percentage of people being CVID screened, (2) the percentage of those being diagnosed, and (3) the effectiveness factor (EF). The EF was calculated by dividing the fraction diagnosed by the fraction screened. It was used as an estimate of how effective testing of these people was compared with testing at random. Only a factor > 1 was considered effective.

All data were stored and processed at Statistics Denmark servers, and no personally identifiable data were accessible. Data handling and statistical analysis were performed using Stata 15.1 (StataCorp LLC, Texas, USA). The study was approved by the Danish Data Protection Agency (Journal nos. 2012-58-0018 and 2013-41-2409). Danish national law does not require ethics approval or individual consent for this kind of research.

Results

We identified a total of 132 patients and 5940 controls ready for analysis (Fig. 1). Approximately 95% of both cases and

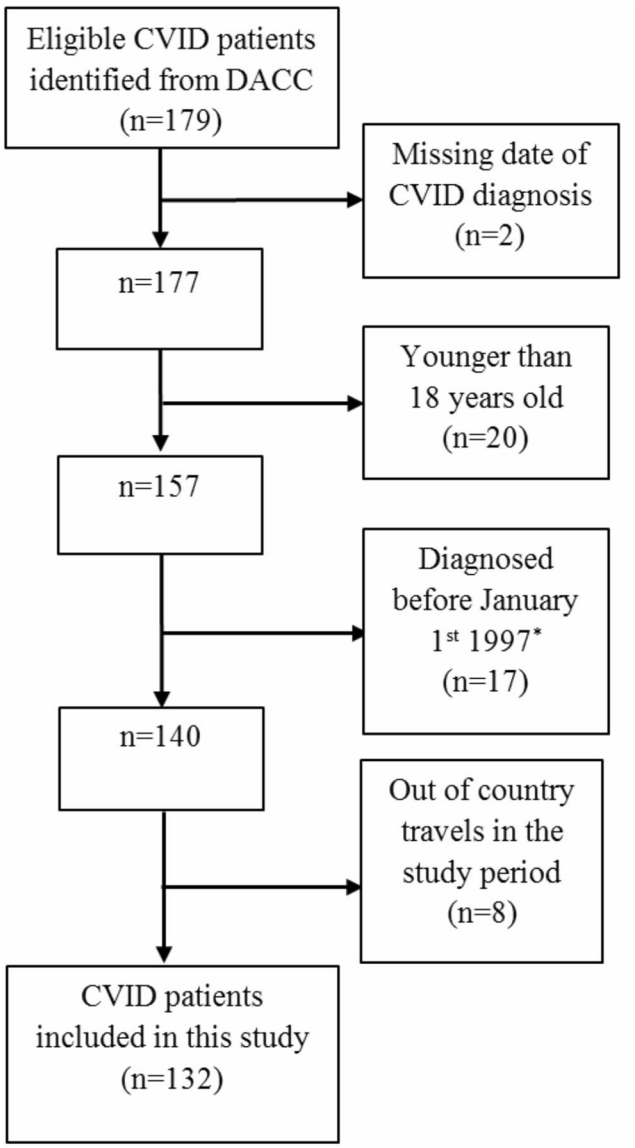


Fig. 1 Case sample flowchart. *Patients diagnosed before January 1, 1997, were excluded as data was first available from 1994 onward. CVID, common variable immunodeficiency; DACC, the Danish Adult Common Variable Immunodeficiency Cohort

controls were Danish-born, 45.5% were males, and the median age at diagnosis of CVID was 47 years (IQR, 35–58.5). At baseline, cases had a statistically significant higher Charlson Comorbidity Index than controls. This difference was mainly due to a higher degree of chronic obstructive pulmonary disease (COPD) (29.6% vs. 3.4%) followed by non-metastatic cancer (6.8% vs. 3.6%) for cases vs. controls. Educational level did not differ between the two groups. In the five Danish regions, a significant difference between cases and controls was observed in two of these (regions of Zealand and Central Jutland). Additional characteristics are provided in Table 1.

During the entire 3-year period before CVID diagnosis, 100% of cases and 96.9% of controls had ≥ 1 consultation. The median number of consultations was more than twice that of the controls in all 3 years (Table 2). This trend was independent of gender, although women had a higher median number of consultations than men, irrespective of case/control status. However, in the last year before diagnosis, the excess number of consultations among cases relative to controls increased substantially among men, leading to a major increase in OR. Overall and regardless of gender, the risk of being diagnosed with CVID increased with the number of consultations, and the association between CVID diagnosis and the number of consultations increased with shorter time to diagnosis (Table 2).

Although there was a trend towards a lower median time to diagnosis with calendar time (1997–2001, 2002–2007, and

Table 1 Baseline characteristics of CVID patients (cases) and matched controls

Baseline characteristics	CVID ($N = 132$)	Controls ($N = 5940$)
Male gender (%)	60 (45.5%)	2700 (45.5%)
Age at the index date, median years (IQR)	47 (35–58.5)	47 (35–58.5)
18–40 years, *n* (%)	50 (37.9)	2250 (37.9)
41–60 years, *n* (%)	54 (40.9)	2430 (40.9)
≥ 60 years, *n* (%)	28 (21.2)	1260 (21.2)
Age at the symptom onset, median years (IQR)	33 (20–47)	–
< 18 years, *n* (%)	27 (20.4)	–
18–40 years, *n* (%)	52 (39.4)	–
41–60 years, *n* (%)	36 (27.3)	–
≥ 60 years, *n* (%)	17 (12.9)	–
Charlson Comorbidity Index, median (IQR)	0 (0–1)	0 (0–0)
0*	72 (54.6)	5069 (85.3)
1–2*	49 (37.1)	763 (12.9)
≥ 3*	11 (8.3)	108 (1.8)
Chronic obstructive pulmonary disease, *n* (%)*	39 (29.6)	201 (3.4)
Non-metastatic cancer, *n* (%)*	9 (6.8)	212 (3.6)
Danish origin, *n* (%)	124 (93.9)	5654 (95.2)
Calendar year of diagnosis (baseline)		
1997–2001, *n* (%)	16 (12.1)	720 (12.1)
2002–2007, *n* (%)	37 (28.0)	1665 (28.0)
2008–2013, *n* (%)	79 (59.9)	3555 (59.9)
Educational level		
High (> 12 years), *n* (%)	37 (28.0)	1548 (26.1)
Medium (12–9 years), *n* (%)	57 (43.2)	2804(47.2)
Low (< 9 years) or unknown, *n* (%)	38 (28.8)	1588 (26.7)
Region of Denmark		
Capital, *n* (%)	40 (30.3)	1810 (30.5)
Zealand, *n* (%)*	7 (5.3)	898 (15.1)
Southern Denmark, *n* (%)	29 (22.0)	1316 (22.7)
Central Jutland, *n* (%)*	42 (31.8)	1316 (22.1)
Northern Jutland, *n* (%)	14 (10.6)	568 (9.6)
Presenting with sinopulmonary infection, *n* (%)	122 (92.4)	–

CVID common variable immunodeficiency, *IQR* interquartile range

*A two tailed *P* value < 0.05

Table 2 Associations between the number of consultations with the general practitioner in the three years before CVID diagnosis and being diagnosed with CVID stratified by gender

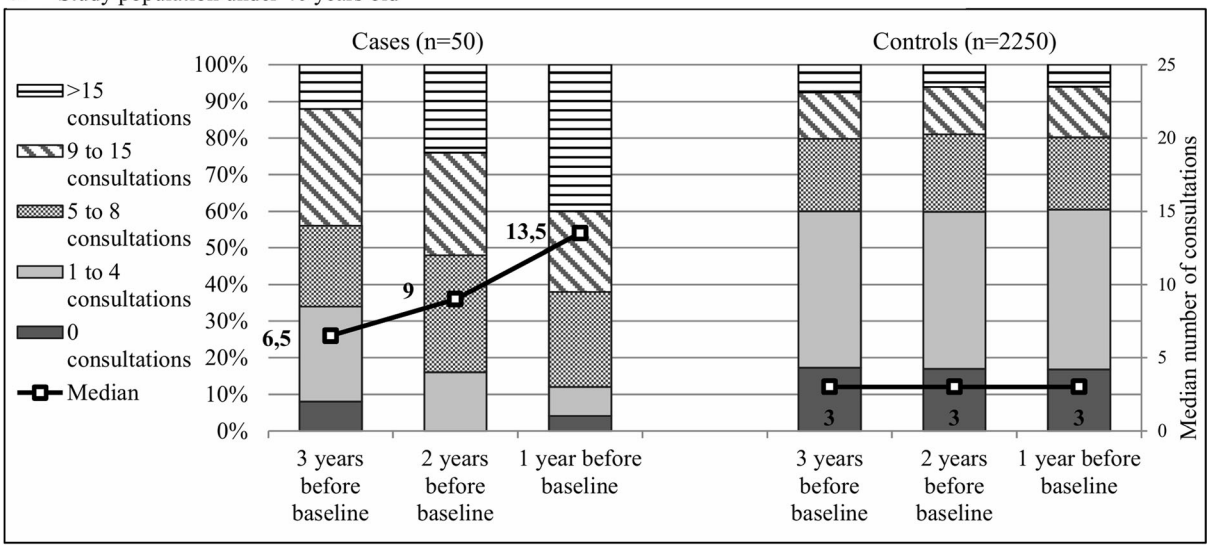
Consultations by GP[1], *n* (%)	CVID versus age- and gender-matched controls			Men			Women		
	CVID (*N* = 132)	Control (*N* = 5940)	CVID vs. controls (OR[2] (95%CI))	CVID (*N* = 60)	Control (*N* = 2700)	CVID vs. controls (OR[2] (95%CI))	CVID (*N* = 72)	Control (*N* = 3240)	CVID vs. controls (OR[2] (95%CI))
Combined consultations in the 3 years before CVID diagnosis, *n* (%)									
Median consultations (IQR)	35.5 (25–66.5)	14 (6–27)	–	28 (18–40.5)	9 (4–18)	–	48 (31.5–80)	20 (10–33)	–
0	0 (0)	182 (3.1)	N/A	0 (0)	146 (5.4)	N/A	0 (0)	36 (1.1)	N/A
1–5	3 (2.3)	1095 (18.4)	0.4 (0.1–1.6)	2 (3.3)	778 (28.8)	0.4 (0.1–1.7)	1 (1.4)	317 (9.8)	1.0 (0.1–9.3)
6–15	10 (7.6)	1917 (32.3)	Ref [1]	7 (11.7)	976 (36.2)	Ref [1]	3 (4.1)	941 (29.0)	Ref [1]
16–30	38 (28.8)	1502 (25.3)	6.3 (3.1–12.7)	25 (41.6)	482 (17.8)	8.3 (3.5–19.4)	13 (18.1)	1020 (31.5)	4.1 (1.2–14.5)
30–45	32 (24.2)	655 (11.0)	14.0 (6.7–29.2)	16 (26.7)	166 (6.2)	17.6 (7.0–44.4)	16 (22.2)	489 (15.1)	11.3 (3.3–38.9)
> 45	49 (37.1)	589 (9.9)	26.8 (13.1–54.9)	10 (16.7)	152 (5.6)	13.6 (4.9–37.4)	39 (54.2)	437 (13.5)	33.6 (10.2–110.4)
Consultations in the year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	15.5 (8–27)	4 (2–9)	–	14.5 (6.5–22.-5)	3 (1–7)	–	16.5 (10–30.5)	6 (3–11)	–
0	2 (1.5)	820 (13.8)	0.5 (0.1–2.2)	2 (3.3)	578 (21.4)	0.7 (0.1–3.5)	0 (0)	242 (7.5)	N/A
1–4	10 (7.6)	2162 (36.4)	Ref [1]	6 (10.0)	1183 (43.8)	Ref [1]	4 (5.6)	979 (30.2)	Ref [1]
5–8	23 (17.4)	1261 (21.2)	5.0 (2.3–10.6)	14 (23.3)	459 (17.0)	7.0 (2.6–18.5)	9 (12.5)	802 (24.8)	2.8 (0.9–9.2)
9–15	31 (23.5)	1036 (17.5)	9.1 (4.4–19.0)	13 (21.7)	300 (11.1)	10.6 (4.0–28.5)	18 (25.0)	736 (22.7)	6.5 (2.2–19.2)
> 15	66 (50.0)	661 (11.1)	35.0 (17.3–70.9)	25 (41.7)	180 (6.7)	42.2 (16.4–108.9)	41 (56.9)	481 (14.8)	24.0 (8.5–68.0)
Consultations in the second year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	11.5 (6–20)	4 (1–9)	–	8 (4–12)	3 (1–6)	–	16 (9.5–23)	6 (3–11)	–
0	0 (0)	863 (14.5)	N/A	0 (0)	586 (21.7)	N/A	0 (0)	277 (8.6)	N/A
1–4	23 (17.4)	2180 (36.7)	Ref [1]	16 (26.7)	1169 (43.3)	Ref [1]	7 (9.7)	1011 (31.2)	Ref [1]
5–8	26 (19.7)	1280 (21.6)	2.2 (1.2–3.9)	17 (28.3)	492 (18.2)	2.7 (1.2–5.4)	9 (12.5)	788 (24.3)	1.7 (0.6–4.5)
9–15	35 (26.5)	1002 (16.9)	4.3 (2.5–7.4)	17 (28.3)	286 (10.6)	5.0 (2.5–10.1)	18 (25.0)	716 (22.1)	3.8 (1.6–9.3)
> 15	48 (36.4)	615 (10.3)	10.2 (6.0–17.5)	10 (16.7)	167 (6.2)	5.4 (2.4–12.4)	38 (52.8)	448 (13.8)	13.8 (6.1–31.5)
Consultations in the third year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	10 (4–18.5)	4 (1–9)	–	6 (3–11)	3 (1–6)	–	14.5 (7–24)	6 (3–12)	–
0	5 (3.8)	845 (14.2)	0.4 (0.2–1.1)	4 (6.7)	611 (22.6)	0.5 (0.2–1.3)	1 (1.4)	234 (7.2)	0.4 (< 0.1–2.9)
1–4	29 (22.0)	2207 (37.2)	Ref [1]	17 (28.3)	1170 (43.3)	Ref [1]	12 (16.7)	1037 (32.0)	Ref [1]
5–8	23 (17.4)	1234 (20.8)	1.5 (0.9–2.7)	17 (28.3)	473 (17.5)	2.6 (1.3–5.1)	6 (8.3)	761 (23.5)	0.7 (0.7–1.8)
9–15	33 (25.0)	1012 (17.0)	3.0 (1.8–5.0)	13 (21.7)	289 (10.7)	3.4 (1.6–7.2)	20 (27.8)	723 (22.3)	2.5 (1.2–5.1)
> 15	42 (31.8)	642 (10.8)	6.4 (3.9–10.7)	9 (15.0)	157 (5.8)	4.5 (1.9–10.5)	33 (45.8)	485 (15.0)	6.5 (3.3–12.8)

CVID common variable immunodeficiency, *GP* general practitioner, *OR* odds ratio, *CI* confidence interval, *IQR* interquartile range, *Ref* reference group

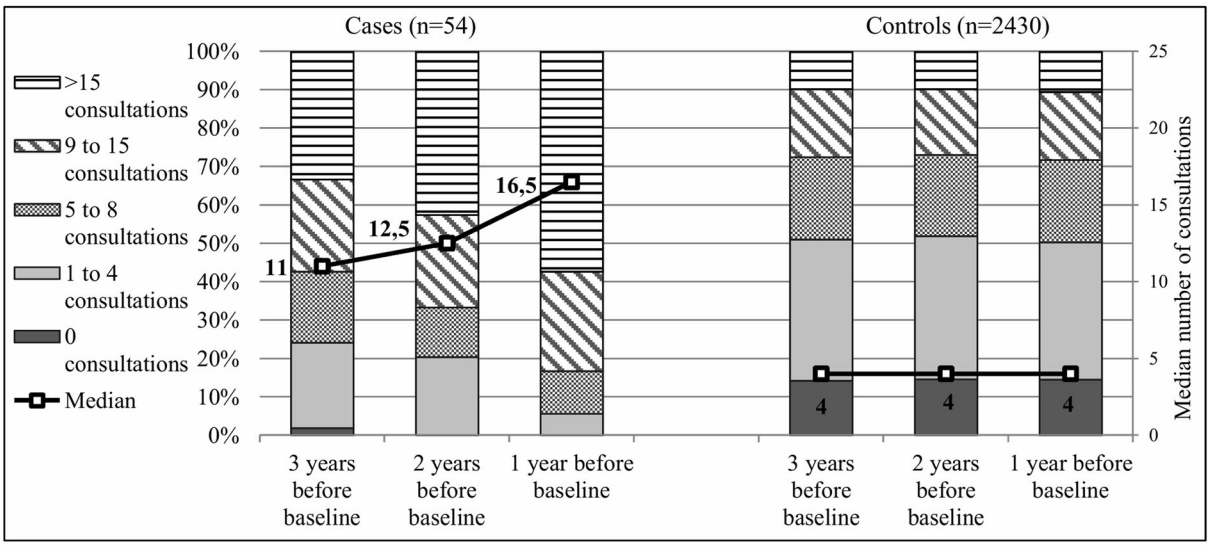
[1] GP—general practitioner, defined by a face-to-face consultation either at the patient's residence or at the clinic or a phone consultation

[2] OR—unadjusted odds ratio calculated by conditional logistic regression, matched on age, gender, and birth year

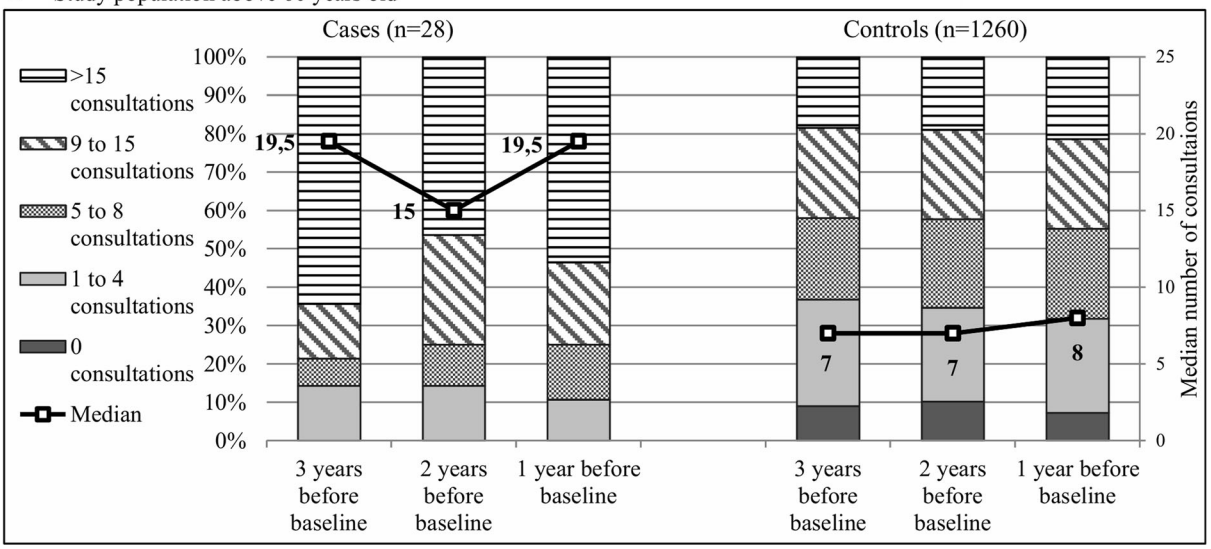
a Study population under 40 years old



b Study population 41 – 60 years old



c Study population above 60 years old



◀ **Fig. 2** Percentage of the study population divided into categories based on annual GP consultations as well as medium number of consultations

2008–2013), the median number of visits for the CVID patients increased in the same period; however, the number of patients was small especially in the first period (supplementary Table 1).

An annual increase in the median number of consultations was observed in patients ≤ 60 years ($n = 104$), in the 3 years before baseline (Fig. 2). In the third year before baseline, patients under 40 years ($n = 50$) had more than twice the median number consultations relative to the controls (6.5 vs. 3), which further increased to more than four times (13.5 vs. 3) in the year leading up to diagnosis. Furthermore, patients aged 18–40 years consulting the GP > 15 times more than tripled from the 3rd year before baseline (12%) to the year before baseline (40%) (Fig. 2a).

Although an increasing number of consultations were associated with an increased risk of a subsequent CVID diagnosis for all age groups, the association was strongest in the individuals ≤ 60 years (Table 3). We found that 18–40-year-old individuals who consulted their doctor 5–8 and 9–15 times and > 15 times compared with 1–4 times in the 3rd year before baseline had an OR of 2.0 (95%CI 0.9–4.4), 5.0 (2.3–10.9), and 3.3 (1.2–9.1) of being diagnosed with CVID, respectively. These ORs increased substantially during the year leading up to CVID diagnosis and decreased with older age (Table 3). However, the numbers were small in all 3 age groups.

When analyzing the exposure as a binary variable (≥ 5, ≥ 10, ≥ 15, and ≥ 30 consultations vs. ≤ 4), we found an overall strong and linear association between the number of consultations and the risk of being diagnosed with CVID for all 3 years and an effectiveness factor > 1 for all measures (Fig. 3). However, although screening of all patients with ≥ 5 consultations in the 3rd year before baseline would identify 74.2% of the undiagnosed patients, it would require that more than 48% of the Danish population was screened with, e.g., immunoglobulin measurements (EF, 1.53). In contrast, these numbers would be 35.6% and 12.2% if only patients with ≥ 15 annual consultations were screened (EF, 2.91).

We found a statistically significant association with all seven examinations analyzed (Table 4). The highest OR was observed in blood testing for inflammation and infection (3rd year: OR 3.8 (95%CI 2.6–5.5), 2nd year: 6.6 (4.6–9.5), and 1st year: 9.0 (6.3–13.0)) whereas the pulmonary function test had the highest EF (from 3.23 to 5.46). Still, despite requiring screening of 3–4% of the population, screening all individuals who had a pulmonary function test would capture 10–20% of the undiagnosed patients.

In the 3rd year before baseline, 74% of the cases visiting the GP had ≥ 1 different examination(s) compared with 50% of the controls. Having ≥ 4 different examinations was associated with an increased risk of a subsequent CVID diagnosis and EF > 1 in all 3 years preceding baseline (3rd year: OR 6.0 (95%CI 3.1–11.5), 2nd year: 7.3 (4.1–13.0), and 1st year: 17.3 (9.6–31.0)) (supplementary Table 1). Furthermore, for cases, the annual median number of the combined amounts of examinations increased as the time to diagnosis decreased (3rd year, 2; 2nd year, 3; 1st year, 5 compared with 1 examination of the controls).

None of the performed sensitivity analyses altered the results substantially.

Discussion

In this population-based nested case-control study, we found that even 3 years before the CVID diagnosis was established, patients had more consultations and examinations by their GP compared with age- and gender-matched controls. The median number of consultations in the case group increased as the time to diagnosis decreased, and more than 96% of all cases consulted their GP every year compared with approximately 86% of the controls. We found a strong association between the number of consultations and the risk of a subsequent CVID diagnosis that was independent of age and gender, but strongest among individuals < 60 years.

Finally, all medical examinations as presented in this study were associated with a subsequent CVID diagnosis, and although screening individuals, who had these examinations performed, would capture a fraction of the undiagnosed CVID patients, none of the examinations would alone or combined be a sufficiently effective measure of identifying a screening population due to either a low procedure prevalence among cases or a relatively high procedure prevalence among controls.

The strengths of our study include the nesting in a nationwide population-based CVID cohort and the use of a well-matched control cohort from the general population. We had full access to Danish registries of high quality, allowing us to (1) look 3 years back in time from the established CVID diagnosis and (2) identify the number of consultations and examinations performed by the GP, thereby removing any recall bias. DCRS allowed us to track every single individual in the 3 years, avoiding any loss to follow-up. No prior studies have to our knowledge attempted to identify patterns for undiagnosed CVID patients in either primary or secondary health care.

Our study has some limitations. Unfortunately, the CVID diagnosis does not alone rely on a test with a positive/negative result. Therefore, the actual time of diagnosis is somewhat arbitrary. Nevertheless, as our results showed strong associations not only for the last year before baseline but also in the second and third year, we presume that any bias might be diluted with time. Although medical records were reviewed to retrieve the CVID diagnoses in DACC, we cannot exclude the possibility of undiagnosed CVID patients in the control

Table 3 Associations between the number of consultations with the general practitioner in the 3 years before CVID diagnosis and being diagnosed with CVID, stratified by age groups

Consultations by GP[1], *n* (%)	Age 18–40 years			Age 41–60 years			Age > 60 years		
	Cases (*N* = 50)	Controls (*N* = 2250)	CVID vs. controls (OR[2] (95%CI))	Cases (*N* = 54)	Controls (*N* = 2430)	CVID vs. controls (OR[2] (95%CI))	Cases (*N* = 28)	Controls (*N* = 1260)	CVID vs. controls (OR[2] (95%CI))
Combined consultations in the 3 years before CVID diagnosis, *n* (%)									
Median consultations (IQR)	30.5 (20–44)	11 (5–20)	–	38 (25–76)	14 (6–27)	–	52.5 (27.5–91.5)	22 (11–40)	–
0	0 (0)	75 (3.3)	N/A	0 (0)	86 (3.5)	N/A	0 (0)	21 (1.7)	N/A
1–5	1 (2.0)	543 (24.1)	0.2 (< 0.1–1.8)	1 (1.8)	434 (17.9)	0.6 (< 0.1–5.4)	1 (3.6)	118 (9.4)	2.4 (0.2–39.0)
6–15	6 (12.0)	818 (36.4)	Ref [1]	3 (5.6)	794 (32.7)	Ref [1]	1 (3.6)	305 (24.2)	Ref [1]
16–30	18 (36.0)	521 (23.2)	6.3 (2.4–16.1)	13 (24.1)	620 (25.5)	6.3 (1.8–22.1)	7 (25.0)	361 (28.6)	6.2 (0.8–50.9)
30–45	15 (30.0)	168 (7.5)	19.3 (7.1–52.2)	15 (27.8)	279 (11.5)	16.6 (4.7–58.3)	2 (7.1)	208 (16.5)	3.3 (0.3–37.2)
> 45	10 (20.0)	125 (5.5)	17.8 (6.2–51.5)	22 (40.7)	217 (8.9)	33.6 (9.8–115.2)	17 (60.7)	247 (19.6)	26.1 (3.8–201.9)
Consultations in the year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	13.5 (7–22)	3 (1–7)	–	16.5 (11–30)	4 (1–9)	–	19.5 (9.5–29.5)	8 (3.5–14)	–
0	2 (4.0)	377 (16.8)	1.2 (0.2–6.6)	0 (0)	352 (14.5)	N/A	0 (0)	91 (7.2)	N/A
1–4	4 (8.0)	982 (43.6)	Ref [1]	3 (5.6)	870 (35.8)	Ref [1]	3 (10.7)	310 (24.6)	Ref [1]
5–8	13 (26.0)	446 (19.8)	9.0 (2.9–28.4)	6 (11.1)	520 (21.4)	3.7 (0.9–14.9)	4 (14.3)	295 (23.4)	1.4 (0.3–6.5)
9–15	11 (22.0)	312 (13.9)	12.5 (3.9–40.4)	14 (25.9)	430 (17.7)	10.5 (3.0–36.8)	6 (21.4)	294 (23.4)	2.3 (0.6–9.5)
> 15	20 (40.0)	133 (5.9)	58.2 (18.6–181.9)	31 (57.4)	258 (10.6)	40.41 (12.1–134.6)	15 (53.6)	270 (21.4)	6.6 (1.8–23.6)
Consultations in the second year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	9 (5–14)	3 (1–7)	–	12.5 (7–21)	4 (2–9)	–	15 (7.5–31)	7 (3–13)	–
0	0 (0)	380 (16.9)	N/A	0 (0)	355 (14.6)	N/A	0 (0)	128 (10.2)	N/A
1–4	8 (16.0)	965 (42.9)	Ref [1]	11 (20.4)	906 (37.3)	Ref [1]	4 (14.3)	309 (24.5)	Ref [1]
5–8	16 (32.0)	476 (21.2)	4.7 (2.0–11.2)	7 (12.9)	514 (21.1)	1.2 (0.5–3.1)	3 (10.7)	290 (23.0)	0.8 (0.2–3.8)
9–15	14 (28.0)	293 (13.0)	7.4 (3.0–18.2)	13 (24.1)	415 (17.1)	2.9 (1.3–6.6)	8 (28.6)	294 (23.3)	2.3 (0.7–8.0)
> 15	12 (24.0)	136 (6.0)	14.5 (5.7–37.2)	23 (42.6)	240 (9.9)	9.0 (4.3–19.1)	13 (46.4)	239 (19.0)	4.9 (1.5–15.6)
Consultations in the third year before CVID diagnosis, *n* (%)									
Median consultations (IQR)	6.5 (4–14)	3 (1–7)	–	11 (6–18)	4 (1–9)	–	19.5 (10–32)	7 (3–13)	–
0	4 (8.0)	387 (17.2)	0.7 (0.2–2.2)	1 (1.9)	344 (14.2)	0.20 (< 0.1–1.6)	0 (0)	114 (9.0)	N/A
1–4	13 (26.0)	964 (42.8)	Ref [1]	12 (22.2)	893 (36.8)	Ref [1]	4 (14.3)	350 (27.8)	Ref [1]
5–8	11 (22.0)	446 (19.8)	2.0 (0.9–4.4)	10 (18.5)	521 (21.4)	1.5 (0.6–3.6)	2 (7.1)	267 (21.2)	0.7 (0.1–3.8)
9–15	16 (32.0)	285 (12.7)	5.0 (2.3–10.9)	13 (24.1)	431 (17.7)	2.4 (1.1–5.4)	4 (14.3)	296 (23.5)	1.3 (0.3–5.3)
> 15	6 (12.0)	168 (7.5)	3.3 (1.2–9.1)	18 (33.3)	241 (9.9)	6.4 (3.0–13.7)	18 (64.3)	233 (18.5)	8.0 (2.6–24.5)

CVID common variable immunodeficiency, *GP* general practitioner, *OR* odds ratio, *CI* confidence interval, *IQR* interquartile range, *Ref* reference group

[1] GP—general practitioner, defined by a face-to-face consultation either at the patient's residence or at the clinic or a phone consultation

[2] OR—unadjusted odds ratio calculated by conditional logistic regression, matched on age, gender, and birth year

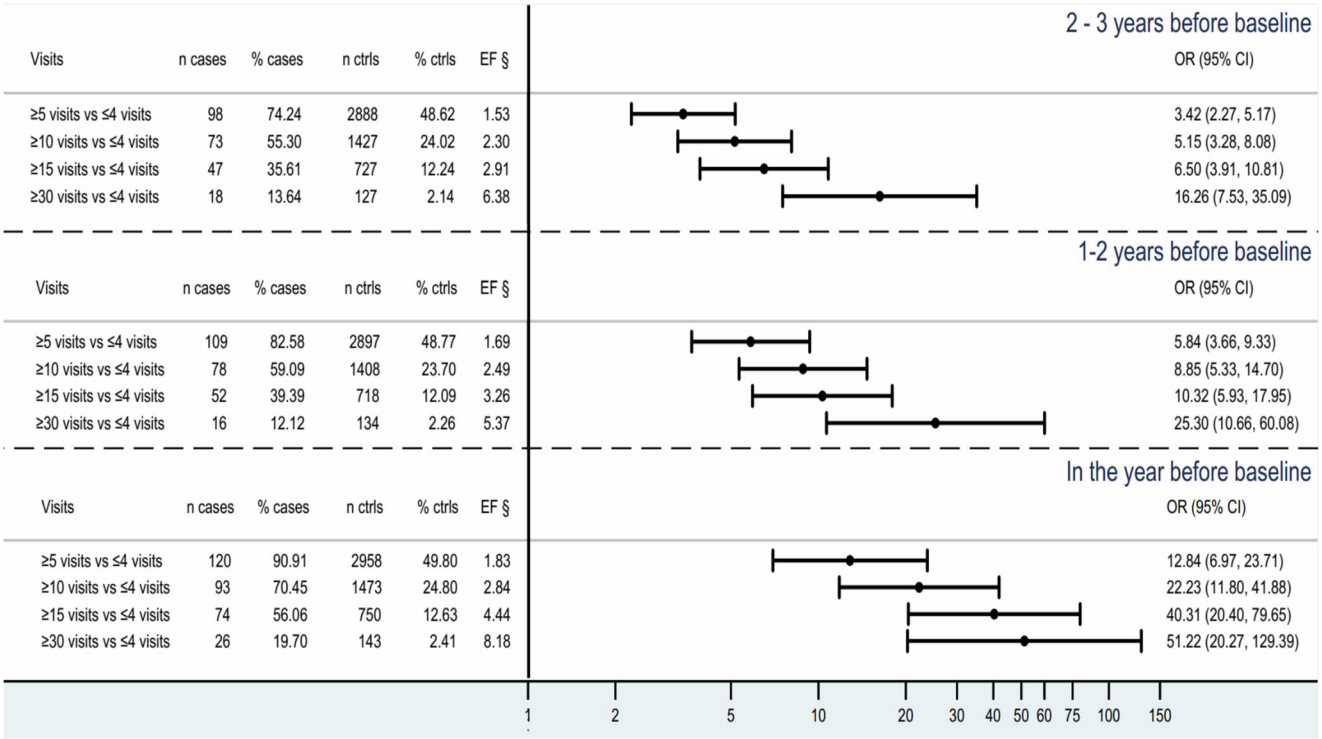


Fig. 3 Forrest plot illustrating the number, percentage, EF, OR, and 95%CI (*x*-axis) for cases and controls with ≥ 5, 10, 15, or 30 visits compared with ≤ 4 visits

group. Nevertheless, as the time of observation in the DACC was long and CVID is a relatively rare disease, we do not believe that this presents a substantial problem. Next, no validation studies of DNHSR have been reported. However, the size, completeness, and degree of accuracy of this register are considered good, as health care services in primary health care are reimbursed from the health care authorities and thus require registration [21]. As DNHSR contains no diagnostic codes, minimal clinical data, and no presumptive diagnosis, we had no information on symptoms or the cause that prompted the GP consultation. Therefore, we had to rely on the number of consultations and performed examinations in the 3 years preceding baseline to describe the contact patterns. We used the same sources of data to attain information on consultations and examinations for both cases and controls, thereby minimizing differential misclassification.

As the limited case population would be further reduced by expanding the timeframe of observation too, e.g., 5 years, the size of the CVID cohort and the start of DNHSR set the limit for the chosen timeframe to 3 years. Nevertheless, due to the progressive behavior of CVID, we believe that substantial disease patterns would be present in the 3 years prior to diagnosis. Our results illustrate a clear pattern already 3 years prior to the diagnosis, and thus further studies could advantageously expand the exposure identification window. We presume that diseases not associated with CVID and other reasons that would prompt a GP consultation (e.g., pregnancies) are equally distributed in the two groups for whom the educational level did not differ substantially (Table 1). Due to the size of the Danish population and the low prevalence of the disease, our study population was unfortunately fairly small. This led to problems with power and thus a risk of type II errors, especially when stratifying data into smaller groups. Nevertheless, our study showed a strong clinically and statistically significant association between multiple consultations and the risk of subsequently being diagnosed with CVID.

Finally, as cases and controls were not matched according to the region that they lived in, a slight difference in the distribution exists (fewer cases than controls lived in Zealand, whereas more cases than controls lived in North Jutland). As both these regions are non-capital areas, we do not believe that this has had a major impact on our results.

The doctors' delay associated with the CVID diagnosis is far too large, and measures to reduce this would be of great importance [3, 7, 9]. The European Society of Immunodeficiencies has published six warning signs for adult primary immunodeficiency (PID), as an attempt to reduce diagnostic delay [5]: (1) four or more infections requiring antibiotics within 1 year, (2) recurrent infections or infection requiring antibiotic treatment, (3) two or more severe bacterial infections, (4) two or more radiologically proven pneumonia within 3 years, (5) infection with unusual localization or unusual pathogen, and (6) PID in the family. In 2016, a study by Arslan et al. [25] evaluated how effective the six warning signs were by screening 3510 patients from the general population. The study found that among 24 patients diagnosed

Table 4 Associations between medical examinations performed at the general practitioner's clinic in the three years before CVID diagnosis and being diagnosed with CVID

Examinations performed by the GP	CVID ($N = 132$)	Control ($N = 5940$)	CVID vs. controls (OR[1] (95%CI))	Effectiveness factor
Examinations in the 3 years before CVID diagnosis, *n* (%)				
Blood tests	102 (77.3)	2862 (48.2)	4.3 (2.8–6.6)	1.60
Blood tests for inflammation/infection[2]	99 (75.0)	1803 (30.4)	7.9 (5.2–11.9)	2.47
Lung function test	40 (30.3)	483 (8.3)	5.1 (3.4–7.5)	3.65
Measurement of hemoglobin	59 (44.7)	1372 (23.1)	2.9 (2.0–4.2)	1.94
Rapid strep A test	41 (31.1)	977 (16.5)	2.4 (1.6–3.6)	1.89
Sending of biological samples excl. blood[3]	68 (51.5)	1325 (22.3)	4.3 (3.0–6.1)	2.31
Urinalysis for urinary tract infections[4]	53 (40.2)	1561 (26.3)	2.0 (1.4–3.0)	1.53
Examinations in the year before CVID diagnosis, *n* (%)				
Blood tests	86 (65.2)	1693 (28.5)	5.8 (4.0–8.6)	2.29
Blood tests for inflammation/infection[2]	78 (59.1)	900 (15.2)	9.0 (6.3–13.0)	3.90
Lung function test	24 (18.2)	198 (3.3)	6.6 (4.1–10.6)	5.46
Measurement of hemoglobin	40 (30.3)	687 (11.6)	3.6 (2.4–5.3)	2.62
Rapid strep A test	18 (13.6)	365 (6.1)	2.5 (1.5–4.1)	2.22
Sending of biological samples excl. blood[3]	34 (25.8)	625 (10.5)	3.2 (2.1–4.8)	2.44
Urinalysis for urinary tract infections[4]	27 (20.5)	743 (12.5)	1.9 (1.2–2.9)	1.63
Examinations in the second year before CVID diagnosis, *n* (%)				
Blood tests	60 (45.5)	1616 (27.2)	2.5 (1.7–3.6)	1.67
Blood tests for inflammation/infection[2]	65 (49.2)	840 (14.1)	6.6 (4.6–9.5)	3.48
Lung function test	16 (12.1)	223 (3.8)	3.7 (2.1–6.3)	3.23
Measurement of hemoglobin	35 (26.5)	650 (10.9)	3.2 (2.1–4.8)	2.42
Rapid strep A test	21 (15.9)	362 (6.1)	3.0 (1.8–4.9)	2.61
Sending of biological samples excl. blood[3]	24 (18.2)	593 (10.0)	2.1 (1.3–3.4)	1.82
Urinalysis for urinary tract infections[4]	30 (22.7)	775 (13.1)	2.1 (1.3–3.2)	1.85
Examinations in the third year before CVID diagnosis, *n* (%)				
Blood tests	59 (44.7)	1590 (26.8)	2.5 (1.7–3.6)	1.67
Blood tests for inflammation/infection[2]	46 (34.9)	794 (13.4)	3.8 (2.6–5.5)	2.61
Lung function test	14 (10.6)	178 (3.0)	3.9 (2.2–6.9)	3.54
Measurement of hemoglobin	27 (20.5)	630 (10.6)	2.3 (1.5–3.6)	1.93
Rapid strep A test	16 (12.1)	431 (7.3)	1.8 (1.0–3.1)	1.67
Sending of biological samples excl. blood[3]	27 (20.5)	527 (8.9)	2.8 (1.8–4.5)	2.31
Urinalysis for urinary tract infections[4]	23 (17.4)	698 (11.8)	1.6 (1.0–2.6)	1.48

CVID common variable immunodeficiency, *GP* general practitioner, *OR* odds ratio, *CI* confidence interval, IQR interquartile range

[1] OR—unadjusted odds ratio calculated by conditional logistic regression, matched on age, gender, and birth year

[2] Blood tests for inflammation/infection include C-reactive protein (CRP), leucocytes, and/or sedimentation rate

[3] Including sending of urine microalbuminuria test and microbiology tests

[4] Urinalysis includes urine stix testing, urine microscopy, urine culture, and/or resistance

with PID and 12 diagnosed with CVID, 83% (20/24 and 10/12) had at least one positive warning sign, respectively. The study concluded that although these warning signs had a high specificity (> 99%) and a high negative predictive value (> 93%) when analyzed individually, the sensitivity was very low (7.8–37%) [25]. In Denmark, similar warning signs are available for the GPs, and even though these are easy to follow, the diagnostic delay of CVID still constitutes a major challenge.

CVID patients with non-infectious complications (i.e., chronic lung disease, cancer, enteropathies, or granulomatous disease) have the highest mortality [8, 26]. Although some of these conditions might be difficult to treat, it seems crucial that these individuals are diagnosed before the development of such conditions. We found that the CVID patient had more than eight times more COPD and almost two times more non-metastatic cancer at baseline than controls. Although we had no data on high-resolution computed tomography scans

concerning bronchiectasis and no data on smoking for the two groups, we presume that the degree of COPD might be a result of recurrent pulmonary infections, which could be slowed down by CVID treatment [11]. However, despite a reduction in the prevalence of sinopulmonary infections due to appropriate treatment, the development of COPD might still occur [11]. COPD in PIDs is well described, and we suggest that young patients with COPD should be tested for hypogammaglobulinemia [27, 28].

As illustrated in our results, healthy young individuals rarely consult their GP, and a substantial association between frequency of consultations and CVID diagnosis was found among young individuals. As the majority of CVID patients have a disease onset before the age of 40 years, it is of great importance to identify these individuals before the development of non-infectious complications [3, 7]. However, identifying the patients via a screening procedure remains a great challenge, as a suitable screening population still needs to be determined.

Studies examining other screening scenarios such as exploring indicator diseases diagnosed in the years before the CVID diagnosis is established, as well as analyzing the quantity of prescribed antimicrobials, could be helpful. As initial steps, we suggest that the GPs should be aware of patients younger than 40 years presenting with multiple consultations due to infections, chronic diarrhea, anemia, neutropenia, or low blood platelets and in those patients measurement of immunoglobulin levels is recommended.

In conclusion, this study adds new knowledge to the pattern of CVID presentation and demonstrates the magnitude of increased morbidity present in patients with CVID several years before the diagnosis. The risk of a CVID diagnosis was highly related to the number of consultations up to 3 years before the diagnosis, and CVID should be a differential diagnosis among patients with multiple GP consultations especially in combination with raised inflammation markers and PFT procedure among patients younger than 40 years.

Acknowledgments The authors of this study greatly appreciate the work of Eva Sandberg and Sören Möller (Odense Patient Data Explorative Network), for independent statistical guidance and supervision, as well as counseling on register-based research conducted in Denmark. We are grateful to all physicians who have provided data to the Danish adult CVID cohort, as well as the patients included in this study. This study could not have been completed without the help of the Danish adult CVID cohort.

Data Availability Statement The datasets for this manuscript are not publicly available as the data on both cases and controls are confidential, and access to the raw data would allow for the identification of personal microdata. To review the raw data, as well as .do files, a data handler agreement with the Danish state (the Danish Data Protection Agency) is needed. If access to the datasets is to be uptrained anyways, a request should be sent to Frederik V. Antonsen (Frederik.veitland.antonsen2@rsyd.dk). The request has to be processed by the Danish Protection Agency, and FA will serve as a correspondent between the parties.

Author Contributions As the principal investigator, FI had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. IJ and LR are responsible for the study concept and design. FI, RI, and LR are responsible for the analysis and interpretation of data. FI is responsible for drafting of the manuscript.FI, LR, RI, TK, AH, CL, IJ, LW, and TN are responsible for the critical revision of the manuscript for important intellectual content. LW, CL, TK, AH, and TN are responsible for obtaining patient data. IJ and LR are responsible for the study supervision.

Funding FI received funding from the University of Southern Denmark as salary for 6 months. The study was mainly funded by the Department of Infectious Diseases at Odense University Hospital and in part funded by an independent grant from Odense University Hospital.

Compliance with Ethical Standards

Conflict of Interest TK has served as a lecturer and attended conferences sponsored by Baxter, Baxalta, Shire, and CSL Behring. CL has served as a lecturer and attended conferences sponsored by Shire, CSL Behring, and Octapharma. AH has received an unrestricted research grant from CSL Behring. All other authors declare that they have no conflict of interest.

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