The burden of disease of idiopathic/genetic generalized epilepsy – A nationwide online survey

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ABSTRACT
The aim of the study was to assess the self-reported burden of disease in people with idiopathic/genetic generalized epilepsy and risk factors associated with high disease burden.

We performed a nationwide online survey on epilepsy characteristics/treatment, quality of life/daily living followed by Standardized Assessment of Personality-Abbreviated Scale, Major Depression Inventory, Barratt Impulsiveness Scale (brief) and the brief Epilepsy Anxiety Survey Instrument. The survey was sent to 275 representative patients with IGE (‘Funen cohort’) and later publicly distributed via the Danish Epilepsy Association.

The characteristics of the responders of the ‘Funen cohort’ \((n=119)\) did not differ from non-responders and previously assessed data. Out of 753 persons accessing the public survey, 167 had probable IGE. As compared to the ‘Funen cohort’, patients from the public survey reported similar age, time since last seizure, years with disease, seizure types, and IGE syndromes but more current and previously tried anti-seizure medications (ASMs). In both cohorts, patients had higher scores for depression, impulsivity, and personality disorders as compared to Danish normal values irrespective of seizure control or medication. Higher depression and anxiety scores but neither impulsivity nor personality disorders were associated with ongoing seizures. Overall health condition was estimated as bad by 28%. In the last four weeks, 20.4% reported limitations of activities of daily living due to epilepsy; 27.8% felt fed up because of their epilepsy. Patients with high subjective disease burden had more current ASMs, shorter time since last seizure and increased scores for depression, anxiety, impulsivity, and personality disorders.

In conclusion, having IGE was associated with higher scores for impulsivity, depression, and personality disorders irrespective of seizure control and current treatment. High subjective disease burden was common and associated with ongoing seizures, absence/myoclonic seizures and high scores for impulsivity, depression, anxiety, and personality disorders.

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1. Introduction

In adults, idiopathic/genetic generalized epilepsy (IGE) comprises Juvenile Myoclonic Epilepsy (JME), Juvenile Absence Epilepsy (JAE), and Epilepsy with Generalized Tonic-Clonic Seizures alone (EGTCS) [1]. Onset is usually in adolescence and although the genetic origin is hardly disputed, the exact etiology remains unknown. IGE is not associated with severe cognitive decline or deficits [2] and the majority of patients achieve seizure control on anti-seizure medication (ASM), although most patients need to try multiple ASMs [3,4]. A minority of patients suffer from drug-resistant epilepsy, which is associated with negative socioeconomic outcome [2] and more psychiatric comorbidities than the background population [5]. However, also patients without recent seizures tend to have fewer children, lower education, employment, and income than healthy controls [5] suggesting that social outcome is not merely determined by seizure control.

Especially patients with JME have been associated with impairment of distinct cognitive functions, impaired decision making...
though multiple studies have shown that patients with IGE, and particular patients with JME, have psychiatric and social difficulties, many studies were likely afflicted with a selection bias toward more severely affected patients. Thus, it remains essentially unknown if the described psychiatric comorbidity is secondary to having a chronic disease or part of the disease spectrum (“endophenotype”) of IGE and JME in particular. Further, the subjective burden of disease, i.e., the perceived impact of having IGE on e.g., the patients’ activities of daily living, has, to the best of our knowledge, no been studied systematically in a large, unbiased cohort.

Therefore, we created a nationwide online survey to investigate patients with IGE’s subjective burden of disease combined with four validated questionnaires screening for anxiety, depression, personality disorders, and impulsiveness. The study aimed at assessing the self-reported burden of disease and factors associated with high burden of disease.

2. Methods

2.1. Survey and questionnaire

The survey was created, stored, and distributed via REDCap [16] hosted by the Open Patient data Explorative Network (OPEN). The Danish version of the questionnaire used and an English translation are available as supplementary data to this article. It comprised questions about three different topics:

(I) Questions about the patient’s epilepsy syndrome and epilepsy treatment.

(II) Questions about current education, work, and the impact of epilepsy on quality of life (from the Quality of Life-31 questionnaire [17]) and activities of daily living (adapted from the Headache impact test [18]).

(III) Four standardized and validated questionnaires: The Barratt Impulsiveness Scale-Brief (BIS-8/BIS-brief) [19], Standardized Assessment of Personality Abbreviated Scale – Adolescent version (SAPAS-AV) [20], Major Depression Inventory (MDI) [21] and The Epilepsy Anxiety Survey Instrument brief version (brEASI) [22]. The brEASI was translated from English to Danish by two independent researchers; a third translator (S.M.) was involved for disaccording propositions. For other scores, Danish translations were available [20,23,24].

2.2. Ethics and approval

All patients answering the questionnaires consented to data processing. In addition, patients from the ‘Funen cohort’ gave informed consent to the use of electronic medical records via a digital mailbox system available in Denmark (e-boks.dk).

2.3. Patient cohort and data collection

The questionnaires were sent to two different cohorts. The ‘Funen cohort’ (named after the Danish island of Funen, where the patients lived at recruitment; \( n = 476 \) patients with verified IGE), which was recently characterized in-depth [5] and is considered near population-based, non-biased and representative. In brief, inclusion criteria for the ‘Funen cohort’ were registered address on Funen at inclusion, age >16, at least one generalized seizure in the patient’s history after the age of ten and typical electroencephalographic (EEG) changes. Electroencephalographic changes were waived in patients with first seizures before the age of 20 and normal magnet resonance imaging (MRI) and classical description of generalized seizures consistent with IGE. Exclusion criteria were all kinds of focal seizures, more than minor focal or background changes in the EEG, MRI with structural abnormalities, or intellectual disability. We recruited patients to the Funen cohort since 2014 (\( n = 492 \) patients), 275 patients gave consent to being contacted for research purpose and were used to validate the survey. A subgroup of patients from the ‘Funen cohort’ completed the BIS-8 as part of a telephone interview between 01.01.2020 and 30.04.2020 as part of a master thesis (L.D.). On 7 December 2020, a link with the survey was sent directly to patients of the ‘Funen cohort’ through their online digital mailbox linked to the patients’ personal registration numbers (e-boks.dk). Patients that did not respond to the initial mail received a reminder two weeks later.

An identical survey was sent to the members of the Danish Epilepsy Association by e-mail (‘Public survey’) on 11th of December 2020 and the 28th of January 2021. All members being diagnosed with epilepsy between the age of 10 and 25 were asked to complete the survey. Further, the survey was published on the Danish Epilepsy Association’s homepage at the beginning of January 2021 and promoted twice using the Epilepsy Associations’ Facebook pages.

2.4. Data cleaning and calculated variables

Data were handled in IBM SPSS version 26.0. Data were cleaned according to a pre-specified protocol. The patients from the ‘Funen cohort’ were diagnosed with IGE and were therefore included irrespective of their subjective assessment of etiology and epilepsy syndrome [2]. In the public survey, the diagnosis of the responders was not known. Therefore, all patients with responses suggestive for another type of epilepsy were excluded from further analysis as shown in Fig. 1.

In the questionnaire, the patients gave “current age”, “year at first seizure”, and “the date for last seizure”. From these data, the parameters “days since last seizure”, “years with disease”, and “age at first seizure” were calculated.

To identify patients with high subjective burden of disease, we combined responses from the following questions: “How often does epilepsy limit your ability to do usual daily activities including household work, work, school or social activities?”

“How often in the past 4 weeks have you been fed up or irritated because of your epilepsy?”

“How good or bad do you rate your health on a scale from 0-100 where 100 is “best imaginable health” and 0 is “worst imaginable health”?”

Persons with high burden of disease were defined as those answering “sometimes”, “often”, or “always” to the first two questions AND rating general health <50. Patients answering both first two questions with “rarely” or “never” AND rating their general health ≥50 were classified as persons with low burden of disease; all other remained unclassified.

Seizure freedom was defined as last seizure for more than 365 days before completing the questionnaire.

For the comparison of responders and non-responders from the previously characterized ‘Funen cohort’, we used standard defini-
tions of syndrome classification and seizure freedom described in [2].

2.5. Statistics

Statistical analyses were predefined in a protocol before data analysis and were performed with IBM SPSS version 26.0, RStudio Desktop 1.4.1106 and Windows Excel version 2016. We used Mann–Whitney U-test for ordinal data (MDI, brEASI, BIS-8, SAPAS-AV), two-sided students t-test for continuous variables and chi-square and z-tests for categorical variables. When applicable, p-values were corrected for multiple testing using Bonferroni-Holm method. For all analyses, p values <0.05 were considered significant. For correlation studies, Pearson’s correlation coefficient was determined.

3. Results

3.1. Validation of questionnaires and patient population

The ‘Funen cohort’ of patients with IGE (n = 476) is considered representative and without substantial bias [2]. Of 275 patients
having agreed to being contacted for research purposes, 119 completed the entire survey and 113 gave consent to use of data from the electronic medical records. To exclude a bias introduced by analyzing responders only, we compared them with non-responders. Key characteristics of patients from the ‘Funen cohort’ responding to the survey and consenting to the use of electronic medical records (n = 113) did not differ from patients that did not respond or did not consent to being contacted (Supplementary Table 1). In this cohort, 85 patients previously completed a BIS-8 as part of a telephone interview as part of a related project [25], which allowed for validating the online survey. The Pearson correlation coefficient of the BIS-8 based on a telephone interview (n = 85) and the current online questionnaire, was 0.64 (p < 0.001); the correlation coefficient was 0.99 (p < 0.001) for current age (Supplementary Fig. 1A and B). Of 119 patients with verified IGE, 4 (3.4%) responded that they do not have IGE and 16 (13.4%) patients were not sure about their diagnosis. Expert-based syndromic diagnosis and patient-perceived syndrome diagnosis were associated, however, with an overlap between syndromes (Supplementary Fig. 1C). In addition, the accordance of the reported seizure types and the seizure types documented in the outpatient clinic medical records was moderate (Supplementary Table 2).

### 3.2. Patient demographics

Table 1 gives an overview of the patients’ demographics in the ‘Funen cohort’ and public survey. The patients with IGE from the public cohort and the responders from the ‘Funen cohort’ reported similar average age (38 years vs. 41 years), average years with disease (7.3 years), and similar distribution of seizure types and syndrome diagnoses (e.g. 33.5% vs. 25.3% JME). In contrast, indicators of disease severity differed slightly, patients from the public cohort with likely IGE diagnosis (Table 1) reported a lower age at onset, a higher number of ASM tried and a higher number of current ASM.

### 3.3. Self-reported burden of disease and psychiatric symptoms

The perceived current burden of having epilepsy is given in Fig. 2A–C. Of the pooled cohorts, 28.4% estimated their overall health condition as bad, 20.4% reported at least sometimes limitations of activities of daily living in the last four weeks; and 27.8% felt fed up or irritated because of their epilepsy in the past four weeks. Responses from patients in the public cohort indicated a more frequent interference of epilepsy with daily activities (Fig. 2B and C).

As compared to the ‘Funen cohort’, patients in the public survey had a higher MDI (‘Funen cohort’: 13.8, public cohort: 17.7, p = 0.003, Mann–Whitney U-test) and brEASI score (‘Funen cohort’: 5.5, public cohort: 6.5, p = 0.03, Mann–Whitney U-test). BIS-8 and SAPAS-AV did not differ (Fig. 2D).

Scores from normal Danish population were available for MDI [23], SAPAS-AV [26] and BIS [24]. In both cohorts, MDI scores were higher than normal population (‘Funen cohort’: 13.8/Public survey: 17.7 vs. normal Danish population: 7.2, Fig. 3B). Thirty-five percent of the patients had MDI scores compatible with depression (defined as MDI > 20; healthy Danish population: 7.1% [23]); 18.5% of the patients had SAPAS-AV scores > 3 indicative for personality disorder (healthy Danish population: 11.3% [26], Fig. 3B). The BIS-8 score of 17.3 both cohorts was within the range of previous

| Table 1 | Demographics for patients in the public survey and from the Funen cohort. |
|----------|-------------------------------------------------------------------------|
|          | Combined cohort | Funen cohort | Public cohort | Public vs. Funen |
|          | Count N(%)/mean | N(%)/mean   | N(%)/mean    | p-value         |
| Age (mean (IQR)) | 39 41 (27) | 38 (22) | n.s.* |
| Age first seizure (mean (IQR)) | 14.08 15.7 | 13.0 | 0.009* |
| Years with disease (mean (IQR)) | 24.93 25.6 (28) | 24.5 | 0.02 |
| Days since last seizure (mean (IQR)) | 2499 2248 (2679) | 2677 (3009) | n.s. * |
| Self-reported IGE syndrome | | | |
| Juvenile myoclonic epilepsy | 81 25 (25.3%) | 56 (33.5%) | n.s. |
| Absence epilepsy | 60 21 (21.2%) | 39 (23.4%) | n.s. |
| Epilepsy with generalized tonic-clonic seizures alone | 118 46 (46.5%) | 72 (43.1%) | n.s. |
| Other kinds of juvenile epilepsy | 7 7 (7.1%) | 0 (0%) | n.s. |
| Absence | No | 119 53 (44.5%) | 66 (39.5%) | n.s. |
| Yes | 167 66 (55.5%) | 101 (60.5%) | n.s. |
| Myoclonic seizures | No | 165 70 (58.8%) | 95 (56.9%) | n.s. |
| Yes | 121 49 (41.2%) | 72 (43.1%) | n.s. |
| Generalized tonic-clonic seizures | No | 44 21 (17.6%) | 23 (13.8%) | n.s. |
| Yes | 242 98 (82.4%) | 144 (86.2%) | n.s. |
| Current number of ASM | 1 | 151 74 (63.8%) | 77 (46.1%) | 0.02 |
| 2 | 76 32 (27.6%) | 44 (26.3%) | 0.09 |
| 3 | 30 6 (5.2%) | 24 (14.4%) | 0.09 |
| 4 | 14 3 (2.6%) | 11 (6.6%) | 0.09 |
| 5 | 0 (0%) | 0 (0%) | 0.09 |
| 6 | 3 1 (0.9%) | 2 (1.2%) | 0.09 |
| Do not know | 9 0 (0%) | 9 (5.4%) | 0.09 |
| Number of ASM tried | 1 | 46 25 (23.1%) | 21 (12.7%) | 0.02 |
| 2 | 56 27 (25%) | 29 (17.5%) | 0.09 |
| 3 | 46 21 (19.4%) | 25 (15.1%) | 0.09 |
| 4 | 36 15 (13.9%) | 21 (12.7%) | 0.09 |
| 5 | 20 7 (6.5%) | 13 (7.8%) | 0.09 |
| 6 | 15 6 (5.6%) | 9 (5.4%) | 0.09 |
| 7 | 12 3 (2.8%) | 9 (5.4%) | 0.09 |
| 8 | 8 1 (0.9%) | 7 (4.2%) | 0.09 |
| More than 9 | 24 3 (2.8%) | 21 (12.7%) | 0.09 |
| Do not know | 11 0 (0%) | 11 (6.6%) | 0.09 |

If not otherwise noted, p values given were determined using two-sided Z test (* t-test, * Wilcoxon rank test). p-values were corrected for multiple testing using Bonferroni-Holm method.
studies on patients with IGE (Fig. 3A) [25,27] and higher than that of healthy population (healthy Danish individuals: BIS-11: 58.6 [24] corresponding to a BIS-8 of 15.0 [25]).

3.4. Seizure control and self-reported psychiatric symptoms

In the combined cohort (n = 286), seizurefreedom in the last year was associated with lower mean MDI scores (seizure free past year: 13.9 vs. seizures past year: 19.4, normal Danish population: 7.2) and lower bEASI scores (seizure free past year: 5.2 vs. seizures past year: 7.4p = 0.001, Fig. 3D). Importantly, MDI scores remained substantially higher than in normal Danish population irrespective of seizure control. In contrast, there was no significant difference in SAPAS-AV score (p = 0.21, Mann–Whitney U-test) and BIS-8 scores (p = 0.65, Mann–Whitney U-test) between patients from this study reporting seizures in the past year and seizure-free patients (Fig. 3C and D). Exploratory analyses of patients with available information on current treatment (n = 103) from the ‘Funen cohort’ did not find associations of MDI scores with ASM treatment incl. levetiracetam treatment (p = 0.53, for current levetiracetam treatment vs. no levetiracetam treatment).

3.5. Risk-factors for high subjective burden of disease

Of the pooled cohort, 68 (23.8%) of the patients fulfilled our definition of high disease burden, 158 (55.2%) answered in the negative on the question about subjective burden of disease and were therefore classified as having low burden of disease. The remainder answered inconsistently (n = 60, 21.0%). Table 2 gives an overview of patients with high and low burden of disease. As compared to patients with a low disease burden, patients with a higher burden of disease had fewer days since last seizure, took and have tried more ASMs, and reported more often myoclonic seizures and absence seizures.

4. Discussion

Our goal was to assess the subjective burden of disease in an unbiased cohort of patients with IGE and find risk factors associated with a high burden of disease. The patients’ responses were valid and consistent and revealed an almost dichotomic pattern given that 79% had either high- or low burden of disease. Around 20% of the patients with IGE reported a high burden of disease, which was associated with increased scores for depression, anxiety, impulsivity, and traits indicative for personality disorders. For those patients, IGE is not a ‘benign disease’ but a disease with substantial impact on life and well-being. Conversely, 55% replied that their epilepsy did not bother them at all. Not surprisingly, high subjective burden of disease was strongly associated with seizure control and more difficult to treat IGE indicated by, for example, a higher number of previous and current ASMs. High-burden of disease was also associated with absence and myoclonic seizures indicative for JME. This is in keeping with a recent register-based study from the same cohort reporting a substantially increased risk of psychiatric disease in IGE and particular patients with JME [5,28]. The association of self-reported JME and burden of disease (uncorrected p-value: 0.02, non-significant after correction for multiple testing, Table 2) has to be interpreted with some care given that the self-reported syndrome diagnosis did not show an optimal concordance with the specialist evaluation, likely due to the well-known difficulties associated with the diagnosis of JME [29]. Conversely, the association is plausible given that the presence of three seizure types is a major risk factor for drug resistance.
which in turn is an important risk factor for high burden of disease.

The second important finding of our study was the high scores for personality disorders, depression, and impulsivity irrespective of seizure control. The scores substantially exceeded the rates seen in the Danish normal population irrespective of the patients’ seizure status. Even patients without seizures in the last year had higher SAPAS-AV, MDI, and BIS-8 scores that were not explained by the use of ASM associated with increased risk of depression like levetiracetam. Though other studies have found similar results regarding anxiety and depression in people with epilepsy, it must be taken into consideration that this study was made during the COVID-19 pandemic [32]. Still, the impact of COVID-19 on well-being and depressive symptoms of the Danish population was very modest, even in the very dramatic early phase [33]. In addition, the majority of questionnaires were completed when most relevant COVID-19-related restrictions were paused or only recently started; thus, a putative COVID-19 effect hardly explains the results.

Previous studies found more psychiatric comorbidities among patients with IGE than among healthy controls [5,34,35]. We found similar results in our psychiatric scores, where BIS-8, SAPAS-AV, and MDI all were higher in our patients compared to those of healthy populations from other studies [23,26,27]. One major challenge of other studies was the recruitment of patients in specialized epilepsy centers, which may be often associated with a substantial selection bias. We here confirm these reports in two independent groups of patients: Patients being representative for a large near-population based cohort, the ‘Funen cohort’, and patients recruited via internet/social media, which likely reflects well-functioning subjects and excludes substantial cognitive deficits. The average time since last seizure of more than 6 years supports this claim and indicates that the cohorts were by no means biased toward more severe cases. Thus, the most likely explanation for the associations are that symptoms of depression, impulsivity, and personality disorders are part of the endophenotype of IGEs [36] and neither secondary to treatment nor seizure control.

One limitation of the study was the use of an online survey and screening questionnaires instead of personal interviews. Screening questionnaires for psychiatric diseases provide information on symptoms only and cannot be used to make a clinical diagnosis. With respect to epilepsy diagnoses, data from an online survey cannot achieve the same validity as an expert diagnosis. We tried to limit these challenges by validating the online survey in the cohort of known patients with IGE (‘Funen cohort’) that received a personal invitation via digital mailbox (e-boks.dk). The public survey distributed via the Danish Epilepsy Patient Association complemented, substantiated, and confirmed these results. Given that >80% of all verified patients with IGE confirmed the IGE diagnosis in the questionnaire, we conclude a low rate of false negative
answers in the public cohort. In contrast, the false-positive rate was more difficult to determine. The high concordance of seizure classification and demographics of patients identified as likely having IGE indicates that the vast majority of the responders to the public survey actually have IGE and that the cohort was representative. Of course, it is difficult to exclude that few patients completed the survey several times and we actually removed few patients with identical responses (Fig. 1). Patients responding to the public survey appeared to have a slightly more severe disease than the ‘Funen cohort’ reflected by higher scores on MDI, bRASI, lower age at onset, fewer days since last seizure, higher number of current or tried ASM, and a higher degree of certainty about diagnosis. If this bias is due to data cleaning or due to the fact that mainly members of the Danish patient association were contacted is difficult to assess. However, the patients included in this study were very similar to the largest and near-population-based Scandinavian cohort of patients with IGE published so far and we therefore assume that the cohorts were representative and without substantial bias.

When screening for symptoms of psychiatric disease, we used only established questionnaires that were available in Danish (apart from bRASI) to allow sound comparisons with other studies. As illustrated by the strong correlation of BIS-8 assessed by telephone and via questionnaire, we are not in doubt about the reliability of the results acquired using an online questionnaire. The difference in BIS-8 and SAPAS-AV scores between patients with and without seizures in the last year did not reach statistical significance. Broader inclusion criteria, different statistical approaches, and a lower sample size are obvious explanations, and we therefore do not think that the results found were conflicting other publications [25].

5. Conclusion

Around one out of five patients with IGE reported a substantial subjective burden of disease mainly associated with seizure burden. However, patients with IGE have higher scores for impulsivity, depression, and personality disorders regardless of seizure frequency or current ASM treatment likely reflecting the endophenotype of IGE.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The study was supported by an unrestricted grant by Eisai to CPB. Eisai had neither influence on study design, data analysis, or reporting. CPB received speakers’ honoraria from Eisai and UCB and was member of an advisory board of Arvelle. The other authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108232.

Table 2

| Clinical characteristics of patients with high and low subjective burden of disease. | High burden of disease | Low burden of disease | p-value |
|---|---|---|---|
| | N (%)/mean | N (%)/mean | |
| Age (mean, (IQR)) | 36 (21) | 41 (27) | n.s.* |
| Age first seizure (mean, (IQR)) | 13.7 (7) | 14.4 (7) | n.s.* |
| Years with disease (mean, (IQR)) | 22.1 (20) | 27.0 (29.25) | n.s.# |
| Days since last seizure (mean, (IQR)) | 1034 (839) | 3296 (4517) | <0.001# |
| Self-reported IGE syndrome | | | |
| Juvenile myoclonic epilepsy | 26 (41.3%) | 37 (24.7%) | n.s. |
| Absence epilepsy | 16 (25.4%) | 36 (24%) | n.s. |
| Epilepsy with generalized tonic-clonic seizures alone | 20 (31.7%) | 72 (48%) | n.s. |
| Other kinds of juvenile epilepsy | 1 (1.6%) | 5 (3.3%) | n.s. |
| Absence | No | 16 (23.5%) | 74 (46.6%) | 0.01 |
| Yes | 52 (76.5%) | 84 (53.2%) | |
| Myoclonic seizures | No | 27 (39.7%) | 99 (62.7%) | 0.01 |
| Yes | 41 (60.3%) | 59 (37.3%) | |
| Generalized tonic-clonic seizures | No | 13 (19.1%) | 25 (15.8%) | n.s. |
| Yes | 55 (80.9%) | 133 (84.2%) | |
| Current number of ASM | | | <0.001 |
| 1 | 23 (33.8%) | 97 (62.2%) | |
| 2 | 24 (35.3%) | 35 (22.4%) | |
| 3 | 11 (16.2%) | 5 (3.2%) | |
| 4 | 8 (11.8%) | 5 (3.2%) | |
| 5 | 0 (0%) | 0 (0%) | |
| 6 | 2 (2.9%) | 1 (0.6%) | |
| Do not know | 0 (0%) | 7 (4.5%) | |
| Number of ASM tried | | | 0.01 |
| 1 | 7 (11.3%) | 34 (22.1%) | |
| 2 | 10 (16.1%) | 37 (24%) | |
| 3 | 6 (9.7%) | 28 (18.2%) | |
| 4 | 6 (9.7%) | 18 (11.7%) | |
| 5 | 9 (14.5%) | 8 (5.2%) | |
| 6 | 3 (4.8%) | 7 (4.5%) | |
| 7 | 10 (16.1%) | 2 (1.3%) | |
| 8 | 1 (1.6%) | 6 (3.9%) | |
| More than 9 | 9 (14.5%) | 10 (6.5%) | |
| Do not know | 4 (6.5%) | 4 (2.6%) | |

If not otherwise noted, p values given were determined using two-sided Z test (* t-test, # Wilcoxon rank test). p-values were corrected for multiple testing using Bonferroni-Holm method.
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