Intensity of Care and Perceived Burden among Informal Caregivers to Persons with Chronic Medical Conditions: A Systematic Review and Meta-analysis

Andrea Carboni-Jiménez[1,2], Danielle B. Rice[1,3], Brooke Levis[4], Mara Cañedo-Ayala[1], Mahrukh Imran[1], Matthew Chiovitti[1], Andrea Benedetti[5-7], Brett D. Thombs[1-3,5,7-9]

[1]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada; [2]Department of Psychiatry, McGill University, Montreal, Quebec, Canada; [3]Department of Psychology, McGill University, Montreal, Quebec, Canada; [4]Centre for Prognosis Research, School of Medicine, Keele University, Staffordshire, UK; [5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; [6]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre; [7]Department of Medicine, McGill University, Montreal, Quebec, Canada, Montreal, Quebec; [8]Department of Educational and Counselling Psychology, McGill University, Montreal, Quebec, Canada; [9]Biomedical Ethics Unit, McGill University, Montreal, Quebec, Canada

Address for Correspondence: Brett D Thombs, PhD Jewish General Hospital; 4333 Cote St-Catherine Road; Montréal, Québec, Canada; H3T 1E4; Telephone: (514) 340-8222 ext. 5112; Fax: (514) 340-8124; Email: brett.thombs@mcgill.ca

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Abstract

Purpose: Informal caregivers provide ongoing assistance to a loved one with a health condition. No studies have compared caregiving intensity and perception of burden across chronic medical conditions.

Materials and Methods: Databases were searched from inception through September 11, 2020 to identify studies that included the Level of Care Index or the Zarit Burden Inventory (ZBI) among caregivers for people with chronic diseases. Pooled mean ZBI scores and 95% confidence intervals by medical condition were calculated using a random effects model and heterogeneity with I^2.

Results: Ninety-seven included articles reported on 98 unique samples across 21 chronic diseases. No study used the Level of Care Index. Among twelve disease groups with more than one study, heterogeneity was too high (I^2 range: 0% to 99.6%, ≥ 76.5% in 11 groups) to confidently estimate burden. The percent of studies rated high risk of bias ranged from 0% to 98%, but all external validity items were rated as high-risk in > 50% of studies.

Conclusions: Findings highlight the need for studies on caregiver burden to improve sampling techniques; better report sampling procedures and caregiver and care recipient characteristics; and develop a standard set of outcomes, including a measure of caregiving intensity.

Systematic Review Registration: CRD42017080962

Keywords: Systematic review; meta-analysis; chronic disease; informal caregivers; perceived burden

Article category: Review

Introduction

Approximately 33% of Canadian adults and 50% of American adults have at least one chronic medical condition [1,2]. People with chronic diseases often depend on the care and support of others, and in many cases this support is provided by informal caregivers. Informal caregivers are people who provide ongoing, unpaid assistance to a family member or friend with a health condition [3]. The support provided by an informal caregiver can include assisting in activities of daily living (ADLs), such as eating and bathing, and instrumental activities of daily living (iADLs) [4], such as managing finances and preparing meals. Caring for a loved one can also involve providing emotional support [3].

Caregiving can be a rewarding experience; however, the delivery of care can also lead to emotional, physical, and financial repercussions [5-7]. A meta-analysis of 84 studies of caregivers of people with dementia, cancer, stroke, and other physical and cognitive impairments, for instance, found that they experienced more stress and symptoms of depression and lower overall well-being, physical health, and self-efficacy than non-caregivers [8]. Another meta-analysis of 23 studies compared 1,594 caregivers of people with dementia to 1,478 matched non-caregivers and found that caregivers had slightly greater risk for health problems than non-caregivers [9].

Within groups of caregivers, the amount of burden reported, including emotional, physical, and financial burden [10], is associated with reduced physical and mental health [11-14], and subjective life expectancy [15]. Caregiver burden is typically defined in one of two ways; objective burden, which refers to the number of hours and type of assistance provided, and subjective burden, which refers to caregivers’ perception of their caregiving experience and the impact of caregiving on their well-being [16].

Various disease group-specific methods have been used to measure objective burden by assessing functional abilities. These include, but are not limited to, the Duke Activity Status Index (DASI) [17], the SCales for Outcomes in Parkinson's disease – Activities of Daily Living (SCOPA-ADL) [18], and the Schwab and England Activities of Daily Living Scale [19]. The Level of Care Index is a measure of objective burden that can be used across disease groups and uses the number of hours spent caregiving per week and the number of ADLs and iADLs provided to classify level of burden as low, medium, or high [20]. For example, in a 2015 study from the United States, 1,248 caregivers of adults requiring assistance with ADLs or iADLs were interviewed, and 58% of caregivers were classified as having medium or high burden [4].

Different methods have been used to assess subjective caregiver burden. The Zarit Burden Interview (ZBI) [21] is a well-validated scale [22]. A meta-analysis of 228 studies of caregivers with a range of care recipient diagnoses, which was conducted to investigate the association between caregiving-related stressors and positive experiences with caregiver burden and depression, reported that the 22-item version of the ZBI (ZBI-22), which was used in 50 of 228 studies, was by far the most commonly used measure of caregiver burden [23]. The mean ZBI-22 score was 29.9 (standard deviation of 9.3) out of a possible 88. ZBI scores were synthesized for all caregivers, regardless of the medical condition of their care recipient, however, and disease-specific results were not reported. Comparing differences in subjective burden across diseases could improve our understanding of the degrees of burden faced by caregivers and how it may vary across diseases.

Much of the existing evidence on caregivers has focused on caregivers of people with mental health disorders, cognitive impairment, and cancer. Less is known about caregiver intensity and the perception of burden among informal caregivers across other chronic diseases that are characterized by their long-term, unremitting nature and burdensome physical symptoms. The objective of the present study was to compare caregiver intensity and burden of informal caregivers of adults with different chronic medical conditions, excluding cancer, mental health conditions, and conditions primarily characterized by cognitive impairment. Specifically, we conducted a systematic review to identify evidence from caregivers of adults with chronic diseases and to compare (1) caregiver intensity as measured by the Level of Care Index and (2) perceived burden as measured by the ZBI.

Materials and Methods

The systematic review and meta-analysis was registered in PROSPERO (CRD42017080962) and was conducted in accordance to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [24].

Study Inclusion Criteria

We included publications of primary studies that reported scores from the Level of Care Index or the data needed to calculate the Index, or the 12- or 22-item versions of the ZBI for informal caregivers of adults (18 years or older) with chronic medical conditions. Studies of any design were eligible. Informal caregivers were defined as persons who provide support or assistance to a friend or family member with a health condition without receiving financial compensation or formal training [3]. They include, but are not limited to, partners, siblings, children, parents, and friends. Eligible chronic medical conditions were defined as permanent conditions that require ongoing follow-up from health professionals over an extended period of time [25]. All caregivers had to be informal caregivers to be included in the review. We excluded studies that reported on informal caregivers of persons with mental health conditions, dementias, or other conditions with cognitive impairment as the prominent characteristic due to the focus on the mental state of the care recipient, which differs from patients with other chronic conditions. We also excluded studies of caregivers of persons with cancer and patients in palliative care because our focus was on caregivers of people living with an ongoing chronic condition; the prognosis of a cancer diagnosis can range from a relatively acute event with ongoing surveillance to a terminal illness, and the focus of caring for patients at the end of life differs dramatically from caring for patients who expect to live for an extended period of time [26]. Studies that included fewer than 10 informal caregivers were excluded.

Search Strategy

Articles for review were identified from the Cochrane Central, CINAHL, EMBASE, MEDLINE, and PsycINFO databases, which were searched from database inception through September 11, 2020. The search terms included "Level of Care Index", "caregiver intensity", and "Zarit Burden Interview". The full search strategy, which was developed and conducted by an investigator with a master's degree in information sciences, is available in the Supplemental Material 1. Searches were not limited by language or publication status. Reference lists of relevant review articles were also manually searched for potentially eligible articles.

Selection of Eligible Studies

Search results were downloaded into RefWorks (RefWorks, Ref-Works-COST, Bethesda, MD, USA), a web-based reference manager, where duplicate publications were removed. Unique references were then transferred to DistillerSR (Evidence Partners, Ottawa, Canada), a systematic review software. Two independent reviewers first evaluated titles and abstracts for eligibility. If either reviewer deemed a citation as potentially eligible based on the title and abstract, a full-text review of the article was completed. Discrepancies between reviewers were resolved through consensus, and through consultation with an independent third reviewer, if necessary, for English, French, and Spanish articles. Articles in other languages were reviewed by a single native speaker working with a team member.

Data Extraction and Synthesis

One reviewer independently extracted data from each included study using a pre-specified extraction form in DistillerSR (see Supplemental Material 2). Variables extracted included author, year of publication, journal, country, chronic disease, recruitment method, number of caregivers and care recipients in the study, number of years since diagnosis, means and standard deviations of the age of caregivers and care recipients, number of female and male caregivers, years of caregiving, the hours of caregiving spent each week, the measure(s) included (Level of Care Index and/or ZBI-12 or ZBI-22), and means and standard deviations of the relevant measure. For randomized controlled trials, baseline outcome scores were extracted. A second reviewer verified the accuracy of all extracted data using the DistillerSR Quality Check function. If published data appeared to include errors, we attempted to contact the corresponding author to clarify; if there was no response, we attempted multiple times to contact co-authors. If there was still no response, we excluded the study.

Risk of bias of included studies was assessed using a tool that was developed to assess risk of bias in population-based prevalence studies [27]. We made minor adaptations to the tool to adapt it for assessing caregiver burden, rather than prevalence (see Supplemental Material 3). The tool includes 10 items, 4 on external validity (representative sample, sampling frame, random selection, non-response bias) and 6 on internal validity (direct data collection, acceptability of case definitions, study instrument, mode of data collection, time of data collection, and calculation). A first reviewer rated each risk of bias item, and a second reviewer verified the accuracy of the assessment. Discrepancies for data extraction and risk of bias rating were solved by consensus with consultation from a third reviewer if necessary, for English, French, and Spanish articles. A single native speaker extracted data and assessed risk of bias for articles published in other languages.

Measures

Caregiver Intensity. The Level of Care Index assesses the intensity of caregiving among informal caregivers [20]. It is determined by calculating the (1) the number of hours spent caregiving per week, (2) the number of instrumental activities of daily living (iADLs; e.g., grocery shopping, managing finances) performed, and (3) the number of activities of daily living (ADLs; e.g. eating and bathing) performed. A number of points (1 to 4) is then allocated based on the number of hours spent caring, and a second number of points (1 to 4) is allocated based on the total number of iADLs and ADLS performed. These two numbers are summed together to obtain a total score that can range from 2-8. Next, caregiver intensity is categorized into five levels of care and three burden categories. Receiving 2-3 points represents level 1 care, and 4 points represents level 2 care, both of which are labelled as “low burden”. Five points represents level 3 care and is labelled as “medium burden”. Six to seven points is categorized as level 4 care and 8 points is level 5 care, and both are labelled as “high burden” [4]. See Supplemental Material 4 for full scoring details.

Burden. The Zarit Burden Interview (ZBI) assesses the perceived burden of caregivers. The long version of the ZBI includes 22 items (ZBI-22), and the short version includes 12 items (ZBI-12). The ZBI-12 is highly correlated with the ZBI-22 with coefficients ranging from 0.92 to 0.97 [28]. Both versions of the tool have also shown strong validity and internal consistency among informal caregivers [29,30]. The ZBI uses a Likert-type scale with a 0 to 4 response format (0 = never and 4 = nearly always) and higher scores represent a higher amount of perceived burden. Scores range from 0-88 for the ZBI-22 and 0-48 for the ZBI-12. There are no established and commonly used cutoff thresholds for categorizing scores on the ZBI-22 or ZBI-12.

Data Analysis

Descriptive statistics used to report the Level of Care Index and ZBI scores included means and standard deviations (SD). In studies in which scores were reported for different treatment or demographic groups (e.g., control and intervention prior to initiating an intervention, spouse and non-spouse), mean ZBI scores were pooled across groups.

Pooled mean ZBI scores and 95% confidence intervals for samples of caregivers of patients with the same chronic condition and for overall scores were estimated using a random effects model [31]. To assess heterogeneity for studies with the same chronic condition, tests using I^2 statistics were performed [32]. All analyses were 2-sided and used an alpha value of 0.05. Analyses were conducted using the statistical software, R (R version 3.6.3; R Studio version 1.2.5042, Foundation for Statistical Computing, Vienna, Austria). We used the metamean function within the meta package for pooling means [33].

Post-hoc analyses were conducted to determine whether mean scores in 85 included studies that used the ZBI-22 were associated with caregiver age (years), percentage of female caregivers, percentage of caregivers as spouses or partners, type of disease (reference = neurological; organ failure; other), country Human Development Index [34] (reference = very high; high; medium), and recruitment setting (reference = outpatient; inpatient; community; mixed; not reported). Other characteristics extracted, such as hours of care provided per week and years of caregiving, were not included in the analyses because few studies reported these data. To do this, we fit a meta-regression model including all covariates at once, using the metareg function in the meta package [33]. To account for missing data that were not reported in some studies, among variables included in the meta-regression, we used multiple imputation by chained equations, using the mice package [35], to generate 20 imputed datasets, weighted by study sample size, using 15 cycles per imputed dataset [36]. Variables in the mice procedure included all of the variables evaluated in the model. Pooled standard errors and associated confidence intervals were estimated using Rubin's rules [37].

Results

There were 3,840 unique titles and abstracts identified from the search. After title and abstract screening, 3,227 citations were excluded, and 613 full-texts were reviewed for eligibility. Ninety-eight articles describing 99 unique samples were initially eligible; however, data reported in one study [38] appeared to include errors (equivalent means and standard deviations reported for age and ZBI-22 scores), and the authors did not respond to several queries to attempt to clarify. Thus, 97 articles were included in the review describing 98 study samples (see figure 1 for flow diagram and Supplemental Material 5 for the list of publications excluded at full-text level, with reasons). All included studies reported subjective burden outcomes for the ZBI-22 or ZBI-12. No studies assessed objective burden using the Level of Care Index or reported the ADL, iADLS, and mean number of hours spent caregiving per week needed to calculate the Level of Care Index. Thirty-five articles used methods other than the Level of Care Index to measure the number or difficulty of ADLs and iADLs performed, but no method was used by more than five studies.

[Insert figure 1 here]

Characteristics of Included Studies

There were 97 articles with 98 samples published in journal articles [39-133], one doctoral dissertation [134], and one conference abstract [135]. Twenty-two study samples (22%) from 21 publications were from North America (Canada [72], Mexico [94], United States [42,43,48,50,52,58,60,71,76,77,92,95,97,99,113,115-118,134]); 5 (5%) were from South America (Brazil [54,55], Chile [46], Colombia [59,135]); 28 (29%) were from Europe (France [45,104,111], Germany [98], Greece [120,121], Ireland [51], Italy [90,91,108], Luxembourg [66], Spain [41,44,53,56,63,83-85,93,96,107], Sweden [68], Switzerland [112], Netherlands [106], United Kingdom [80,82]), 30 (31%) were from Asia (China [64,73,74,81,122,123], India [57,109,124], Iran [62,103,125-127], Japan [70,101,110,114,128], Jordan [129], Malaysia [130], Pakistan [100], Saudi Arabia [40], Singapore [67,131], South Korea [69,79,87,102], Vietnam [132]), 8 (8%) were from Turkey [39,49,61,65,86,88,89,133], and 2 (2%) were from Australia and New Zealand [47,75]. Three publications (3%) included caregivers across multiple countries [78,105,119].

Publications reported on caregivers of people with 21 chronic diseases. There were more than one study sample on caregivers of people with Parkinson’s disease (N = 26, 27%), chronic kidney disease (N = 19, 19%), heart failure (N = 10, 10%), multiple sclerosis (N = 9, 9%), amyotrophic lateral sclerosis (N = 7, 7%), spinal cord injury (N = 5, 5%), chronic obstructive pulmonary disease (N = 4, 4%), epilepsy (N = 3, 3%), cirrhosis (N = 2, 2%), diabetes mellitus (N = 2, 2%), and essential tremor (N = 2, 2%) (table 1). One article included caregivers for two different diseases [98].

[Insert table 1 here]

The studies included a total of 12,397 informal caregivers (table 2). Sixty-two percent of caregivers were female, and the mean age was 53 years (standard deviation [SD] = 14). Most caregivers (68%) were caring for a spouse or partner. They reported caregiving for a mean of 7 years (SD = 6) and 41 hours (SD = 30) per week. Eighty-five study samples (87%) assessed perceived burden of informal caregivers using the ZBI-22. Among the 85 study samples, 46 recruited participants from outpatient settings (e.g., outpatient clinics), 5 studies from inpatient settings (e.g., hospitalized patients), 9 from community settings (e.g., patient organizations), 6 from mixed settings (i.e., a combination of two or more settings, such as outpatient clinics and community support groups), and 19 did not report recruitment setting (see Supplemental Material 6). Thirteen studies (13%) used the ZBI-12. Caregivers reported a pooled mean score of 30.6 (95% CI: 27.8 to 33.4) on the ZBI-22 (N = 11,139) and a pooled mean score of 12.6 (95% CI: 9.1 to 16.0) on the ZBI-12 (N = 1,258; table 3).

[Insert table 2 here]

Outcomes

Table 3 shows pooled mean subjective burden scores for the ZBI-22 and ZBI-12 by medical condition. For caregivers assessed with the ZBI-22, caregivers of patients living with rheumatoid arthritis reported the highest degrees of subjective burden. Among eight disease groups with more than one study using the ZBI-22 (N participants per disease group range 265 to 3,034), caregivers of adults with spinal cord injury reported the highest levels of burden, followed by caregivers of adults with chronic kidney disease, chronic obstructive pulmonary disease, heart failure, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease. However, there was low precision of estimates, based on wide confidence intervals and high I^2 values (heterogeneity) across disease groups. For those assessed with the ZBI-12, caregivers of patients living with diabetes mellitus reported the highest degrees of subjective burden. Four disease groups included more than one study using the ZBI-12 (N range 155 to 266), with caregivers of patients with heart failure reporting greater levels of burden, followed by caregivers of patients with cirrhosis, spinal cord injury, and essential tremor. All eight chronic disease groups with more than one study using the ZBI-22 showed considerable heterogeneity ($I^2 > 75\%$; range: 96.0% to 99.6%, table 3) [136], while the chronic diseases groups with more than one study using the ZBI-12 showed a wide range of heterogeneity scores (range: 0% to 95.6%; table 3). There was considerable heterogeneity across disease groups (I^2 for all ZBI-22 studies = 99.2% and I^2 for all ZBI-12 studies = 98.3%; table 3).

[Insert table 3 here]

Meta-regression

Meta-regression analyses found one significant association: compared to outpatient settings, ZBI-22 scores were an average of 10.19 (95% CI: 0.13 to 20.25) points higher in community settings (see table 4). Grouping variables by study are available in the Supplemental Material 6.

[Insert table 4 here]

Risk of Bias

As shown in table 5, the percent of items rated as high risk of bias ranged from 0% (0 of 98 study samples) for two internal validity items, study instrument and calculations, to 98% (96 of 98 studies) for sampling frame, an external validity item. All 4 external validity items were rated as high-risk in greater than 50% of studies, including 1) the representativeness of the caregiving sample in relation to relevant variables (e.g., age, sex, severity of medical condition), which was rated as high-risk in 62 studies (63%); 2) the sampling frame, rated as high-risk in 96 studies (98%); 3) the use of random selection or a census, rated as high-risk in 89 studies (91%); and 4) non-response bias (response rate <75%), rated as high-risk in 63 studies (64%). The percent of items rated high risk among the 6 that evaluate internal validity ranged from 0% to 41% (40 of 98 study samples).

[Insert table 5 here]

Discussion

The current study compared levels of subjective burden perceived by 12,397 informal caregivers of people living with 21 different chronic diseases. We did not identify any studies that reported objective burden as measured by the Level of Care Index. Eighty-five of 98 included study samples assessed subjective burden with the ZBI-22, and thirteen used the ZBI-12. Caregivers (N = 11,139) reported a pooled mean ZBI-22 score of 30.6 (95% CI: 27.8 to 33.4) and a pooled mean (N = 1,258) ZBI-12 score of 12.6 (95% CI: 9.1 to 16.0). There was considerable heterogeneity, however, overall (ZBI-22 I^2: 99.2%; ZBI-12 I^2: 98.3%) and within disease groups (I^2 range ZBI-22: 96.0% - 99.6%; I^2 ZBI-12 range: 0% - 95.6%).

Risk of bias evaluations and meta-regression analyses were conducted in order to attempt to understand the heterogeneous burden results. Meta-regression analyses found one significant association: compared to outpatient settings, ZBI-22 scores were an average of 10.19 (95% CI: 0.13 to 20.25) points higher in community settings compared to outpatient samples.

One possible explanation for the association of community settings with substantially higher scores may be explained by how participants in these studies were recruited. They were typically convenience samples of a select group of participants who wished to participate in a study of caregivers and caregiver burden, which may suggest that these studies included a disproportionate number of caregivers with elevated burden who were actively searching for support or information. For example, there were studies in which caregivers were recruited from patient organizations of which they were members [68], who contacted research groups after seeing advertisements [99], or who were contacted through disease-related educational symposiums that they attended [91]. In outpatient settings, conversely, caregivers were usually approached during appointments attended with their care recipient [e.g., 58,66,69].

Risk of bias ratings may also provide insight into the heterogeneity across studies. All four items related to sampling (external validity) were rated as high-risk in more than 50% of included studies. The representativeness of the caregiving sample in relation to caregiving variables (e.g., age, sex, severity of medical condition) was rated as high risk in 63% of studies. Studies' eligibility criteria were often not reflective of the targeted population of caregivers (e.g., only included participants caring for a parent [49]) or did not report important demographic data (e.g., age, sex, relationship type). The sampling frame was also rated as high risk in 98% of studies, indicating that caregivers were usually only sampled from one hospital, city, or country, limiting generalizability of results. Among 91% of studies, the lack of use of a census or consecutive or random sampling resulted in a rating of high risk, as most studies relied on convenience sampling. Finally, non-response bias was rated as high risk in 64% of studies. This reflected that most studies did not meet a minimum response rate of 75% or greater or did not conduct an analysis showing that responders and non-responders were similar.

The heterogeneity found across and within disease groups makes comparisons with other diseases, specifically, mental illness, cognitive impairment, and cancer, difficult. Systematic reviews and meta-analyses of such groups that have examined factors associated with burden have found similar issues as in the present review, including inconsistent definitions of burden, inconsistent reporting of patient characteristics, and the inclusion of low-quality studies [137-140]. We did not identify any systematic reviews in mental illness, cognitive impairment or cancer that reported and synthesized evidence on levels of burden.

It may be possible to identify similar predictors of caregiver burden across some conditions (e.g., lower caregiver and patient health-related quality of life in amyotrophic lateral sclerosis and Parkinson’s disease) [83,141], but there are specific challenges unique to different diseases that may impact the caregiving experience [141-145]. For that reason, it is recommended that subjective burden and factors associated with burden in diverse patient populations be considered separately by medical conditions and that heterogeneity be addressed and considered in interpretation of results.

The Level of Care Index, created by the National Alliance for Caregiving, is an objective measure of burden that relies on established measures of functioning, ADLs and iADLs [20,146]. In the current review, although 35 publications measured the number or difficulty of ADLs and iADLs performed, no method was used more than five times. Some studies used disease-specific measures (e.g., SCOPA-ADL), while others reported the number of ADLs and iADLs performed, without reporting the number of weekly hours spent caregiving.

There is no current established core outcome set in the caregiving literature [147,148] and further high-quality studies of caregiver burden are needed. Reporting the Level of Care Index or the data needed to calculate it could provide a way to standardize assessment of the impact of a disease on caregivers and better compare across studies and diseases. This, combined with more consistent reporting of caregiver and care recipient characteristics, including age, sex, relationship type, years lived with the disease, and years caregiving, would improve the evidence-base and our ability to identify factors associated with greater caregiver burden. Ideally, an agreed upon conceptual model of data elements that should be collected would be developed to guide study design.

Limitations

Several limitations should be considered when interpreting results of the study. First, all studies were rated as at high risk of bias for at least 1 of 4 risk of bias items that assess sampling and external validity. Second, the disease types were heterogeneous and limited our ability to compare between diseases. Third, the studies within each disease group also showed considerable heterogeneity, which also limited our ability to draw conclusions about burden within a disease. Fourth, studies with diverse eligibility criteria for care recipients were included (e.g., age, progression of disease). Fifth, many studies did not adequately report the characteristics of included caregivers. Sixth, we included studies that reported means and standard deviations and excluded studies that only provided medians; however, only six otherwise eligible studies were excluded for this reason. Seventh, no studies included the Level of Care Index. Various disease specific measures were used to measure objective burden which did not allow for between study comparisons of caregiver intensity. Finally, while different methods of assessing subjective burden are used [23], we limited our search to the ZBI, and we do not know the degree to which our findings generalize to studies that used other measures.

Conclusions

The findings of this study underline the need for studies on caregiving to improve sampling techniques and reporting of sampling procedures, for better reporting of caregiver and care recipient characteristics, and for the development of a standard set of characteristics and outcomes to collect and report. Included in this, the use of an objective measure of caregiving intensity, such as the Level of Care Index, would facilitate comparisons. Improving these aspects of studies on caregiver burden would increase our ability to compare perceived burden across diseases and to identify factors associated with vulnerable caregivers. Improving the evidence base through better methodology and reporting would also improve our ability to work with vulnerable caregiver groups to develop and test interventions tailored to address their needs.

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Figure list.

Table 1. Study characteristics

Study (first author, year)	**Caregiver variables**										**Care recipient variables**		
				Relationship to care recipient, n (%)									
	Number of care recipients and caregivers who completed the ZBI-12 or -22	**Females, n (%)**	**Age in years, mean (SD)**	**Spouse or partner**	**Child**	**Parent, sibling, friend, other or not specified (NS)**	**Hours of care per week, mean (SD)**	**ZBI version**	**ZBI score, mean (SD)**	**95% confidence interval**	**Females, n (%)**	**Age in years, mean (SD)**	**Years lived with the disease, mean (SD)**
Amyotrophic lateral sclerosis													
Bentley, 2014 [47]	18	13 (72)	NR[a]	18 (100)	0 (0)	0 (0)	NR	12	12.4 (7.9)	8.8 – 16.0	NR	NR	NR
Burke, 2018 [51]	85	60 (71)	55 (13)	63 (74)	16 (19)	Other relatives = 6 (7)	46 (47)	22	26.7 (14.4)	23.6 – 29.8	34 (40)	64 (11)	NR
Geng, 2017 [64]	81	55 (68)	48 (14)	55 (68)	0 (0)	NS = 26 (32)	NR	22	26.8 (15.1)	23.5 – 30.1	32 (40)	53 (12)	1 (1)
Kim, 2011 [79]	89	68 (76)	53 (13)	66 (74)	12 (13)	Parent = 5 (6); NS = 6 (7)	NR	22	54.1 (14.3)	51.1 – 57.1	25 (28)	59 (11)	NR
Oh, 2018 [87]	202	123 (61)	51 (14)	134 (67)[b]	49 (25)	Parent = 6 (3); NS = 11 (6)	NR	22	43.1 (19.5)	40.4 – 45.8	97 (48)	57 (11)	4 (8)
Pagnini, 2010 [90]	40	28 (70)	56 (12)	33 (83)	6 (15)	Other relative = 1 (3)	NR	22	19.5 (15.5)	14.7 – 24.3	16 (40)	62 (12)	NR
Thomas, 2018 [109]	30	NR	46 (10)	22 (73)	2 (7)	Sibling = 1 (3); parent/other relative = 5 (17)	NR	22	12.9 (11.6)	8.7 – 17.1	11 (37)	53 (11)	1 (NR)
Celiac disease													
Roy, 2016 [95]	94	29 (31)	NR	94 (100)	0 (0)	0 (0)	NR	22	17.5 (12.8)	14.9 – 20.1	67 (71)	NR	NR
Chronic obstructive pulmonary disease													
Badr, 2017 [42]	89	68 (76)	55 (16)	35 (39)	25 (28)	Friend = 3 (3); other relative = 6 (7); NS = 20 (22)	5 (1)	22	21.0 (13.6)	18.2 – 23.8	54 (61)	68 (8)	NR
Cain, 2000 [52]	138	118 (86)	59 (14)	96 (70)	0 (0)	Other relative = 42 (30)	NR	22	24.4 (13.8)[c]	22.1 – 26.7	NR	NR	NR
Fernández-García, 2020 [63]	99	90 (91)	NR	49 (49)	0 (0)	NS = 50 (51)	NR	22	51.4 (14.2)	48.6 – 54.2	58 (23)	69 (10)	NR
Göriş, 2016 [65]	112	84 (75)	NR	NR	NR	NR	NR	22	40.9 (20.6)	37.1 – 44.7	45 (40)	NR	NR
Cirrhosis													

Bajaj, 2011 [43]	58[d]	69 (66)[e]	51 (14)[f]	93 (89)[g]	6 (6)[h]	Friend = 5 (5)[i]	NR	12	11.5 (8.4)	9.3 – 13.7	31 (30)	59 (6)	8 (4)
Hareendran, 2020 [124]	132	117 (89)	41 (10)	99 (75)	22 (17)	Parent = 3 (2); sibling = 8 (6)	NR	12	14.0 (5.8)	13.0 – 15.0	NR	51 (9)	NR
Diabetes mellitus													
Çamur, 2020 [133]	139	109 (78)	57 (9)	66 (47)	56 (40)	Parent = 7 (5); sibling = 11 (8)	NR	12	28.3 (8.5)	26.9 – 29.7	45 (32)	73 (7)	NR
Hirakawa, 2008 [70]	228	166 (73)	64 (13)	108 (47)	69 (30)	Sibling = 9 (4); daughter or son-in-law = 41 (18); NS = 1 (<1)	NR	22	29.2 (16.5)	27.1 – 31.3	135 (59)	79 (7)	NR
Chronic kidney disease													
Abed, 2020 [129]	88	64 (73)	41 (14)	32 (36)	33 (38)	NS = 23 (26)	NR	12	14.4 (8.9)	12.5 – 16.3	46 (52)	55 (17)	5 (5)
Al Wakeel, 2016 [40]	105	78 (74)	39 (10)	0 (0)	0 (0)	Spouse/child = 75 (71); NS = 30 (29)	NR	22	46.8 (23.2)	42.4 – 51.2	60 (57)	52 (14)	4 (9)
Alvarez-Ude, 2004 [41]	221	170 (77)	57 (15)	156 (71)	32 (14)	Parent = 16 (7); sibling = 6 (3); NS = 10 (5)	NR	22	42.9 (14.2)	41.0 – 44.8	71 (32)	60 (16)	NR
Bañobre González, 2005 [44]	25[j]	NR	NR	NR	NR	NR	NR	22	30.7 (22.5)	21.9 – 39.5	15 (56)	65 (15)	2 (2)
Carmona Moriel, 2015 [53]	18	12 (67)	NR	NR	NR	NR	103 (68)	22	39.2 (11.5)	33.9 – 44.5	6 (33)	67 (16)	NR
Farzi, 2019 [126]	254	184 (72)	48 (13)	129 (51)	68 (27)	Parent = 22 (9); sibling = 24 (9); grandchild = 11 (4)	63 (25)	22	45.0 (6.8)	44.2 – 45.8	159 (63)	54 (13)	5 (4)
Griva, 2016 [67]	111[k]	82 (76)[l]	46 (14)	44 (40)	56 (50)	Parent = 1 (1); sibling = 2 (2); other relatives = 3 (3); NS = 5 (5)	NR	22	27.5 (14.9)	24.7 – 30.3	124 (54)	60 (12)	3 (3)
Hoang, 2019 [132]	178	99 (56)	45 (14)	105 (60)[m]	36 (21)[n]	Sibling = 8 (5); child-in-law = 5 (3); parent/grandparent = 21 (12)[o]	NR	22	40.2 (10.5)	38.7 – 41.7	NR	NR	NR
Kilic, 2017 [78]	210	145 (69)	NR	87 (41)	85 (40)	Sibling/grandchild = 38 (18)	NR	22	39.4 (12.4)	37.7 – 41.1	NR	NR	NR
Mollaoğlu, 2013 [86]	122	98 (80)	52 (9)	80 (66)	0 (0)	Child/daughter-in-law/sibling = 42 (34)	NR	22	55.0 (7.6)	53.7 – 56.3	NR	NR	NR
Paschou, 2018 [120]	50	38 (76)	62 (11)	50 (100)	0 (0)	0 (0)	NR	22	27.3 (18.3)	22.2 – 32.4	12 (24)	66 (10)	9 (7)
Shah, 2017 [100]	164	97 (59)	45 (11)	112 (68)	43 (26)	Other relatives = 10 (6)	NR	22	31.4 (12.3)	29.5 – 33.3	NR	NR	2 (1)[p]
Shimoyama, 2003 [101]	22[q]	14 (64)	51 (12)	17 (77)	3 (14)	Parent = 2 (9)	NR	22	12.5 (11.8)	7.6 – 17.4	9 (36)	50 (15)	NR
Sotoudeh, 2019 [103]	70	55 (79)	46 (14)	35 (50)	29 (41)	NS = 6 (9)	NR	22	69.5 (9.1)	67.4 – 71.6	NR	NR	NR
Teixidó-Planas, 2018 [107]	107	89 (83)	58 (15)	83 (78)	17 (16)	Parent = 5 (5); NS = 2 (2)	NR	22	25.5 (16.1)	22.4 – 28.6	31 (29)	63 (13)	NR

Washio, 2012 [114]	108	83 (77)	63 (12)	67 (63)[r]	0 (0)	NS = 40 (37)[s]	38 (49)[t]	22	29.3 (19.2)	25.7 – 32.9	49 (45)	74 (7)	NR
Wicks, 1997 [115]	96	73 (76)	47 (11)	51 (62)[u]	0 (0)	NS = 31 (38)[v]	NR	22	19.8 (11.5)	17.5 – 22.1	NR	NR	NR
Wicks, 1998 [116]	19	15 (79)	42 (10)	16 (84)	0 (0)	NS = 3 (16)	NR	22	23.1 (8.1)	19.5 – 26.7	NR	44 (10)	1 (1)
Zhang, 2020 [123]	170	97 (57)	54 (14)	110 (65)	52 (31)	Parent = 5 (3); NS = 3 (2)	NR	22	30.0 (12.6)[w]	28.1 – 31.9	88 (52)	62 (14)	NR
Epilepsy													
Han, 2015 [69]	391	NR	NR	164 (44)[x]	0 (0)	Parent = 191 (51); NS = 20 (5)[y]	NR	22	43.8 (26.7)	41.2 – 46.4	187 (48)	39 (15)	14 (13)
Karakis, 2014 [76]	48[z]	33 (69)	46 (13)	28 (58)	0 (0)	Parent/sibling = 18 (38); NS = 2 (4)	11 (21)	22	20.0 (14.5)	15.9 – 24.1	74 (59)	38 (13)	15 (14)
Lai, 2019 [130]	111	80 (72)	52 (14)	22 (20)	7 (6)	Parent = 61 (55); sibling = 15 (14); NS = 6 (5)	78 (62)[aa]	22	29.9 (16.1)	26.9 – 32.9	51 (46)	38 (15)[bb]	NR
Essential tremor													
Ceronsky, 2019 [118]	98	63 (64)	71 (12)[cc]	61 (62)	22 (22)	Sibling = 2 (2); friend = 10 (10), other relative = 3 (3)	NR	12	5.3 (6.5)	4.0 – 6.6	54 (55)	81 (9)	42 (23)
Kellner, 2017 [77]	57	35 (65)	67 (13)	31 (54)	17 (30)	Friend = 5 (9); niece/girlfriend/daughter-in-law = 4 (7)	5 (10)	12	6.4 (8.4)	4.2 – 8.6	36 (63)	77 (10)	36 (22)
Heart failure													
Bozkurt Zincir, 2014 [49]	138	90 (65)	37 (12)	0 (0)	138 (100)	0 (0)	NR	22	37.4 (7.8)	36.1 – 38.7	75 (54)	66 (13)	NR
Chung, 2010 [58]	109	82 (75)	57 (13)	86 (79)	10 (9)	Friend = 5 (5); son or daughter-in-law = 5 (5); other relative = 3 (3)	NR	22	15.8 (11.8)	13.6 – 18.0	44 (40)	61 (12)	NR
Etemadifar, 2014 [62]	87	70 (80)	41 (9)	25 (29)	50 (57)	Parent = 4 (5); sibling = 8 (10)	NR	22	56.6 (6.8)	55.2 – 58.0	33 (38)	61 (11)	NR
Ghasemi, 2020 [127]	140	86 (61)	39 (13)	27 (19)	69 (49)	Parent = 16 (11); sibling = 14 (10); NS = 14 (10)	NR	22	31.5 (13.9)	29.2 – 33.8	NR	70 (16)	NR
Hooker, 2018 [71]	99	80 (81)	57 (16)	69 (70)	26 (26)	Friend = 2 (2); NS = 2 (2)	NR	12	13.1 (8.3)	11.5 – 14.7	21 (21)	66 (12)	NR
Hooley, 2005 [72]	50	40 (80)	61 (14)	33 (66)	0 (0)	Other relatives = 15 (30); NS = 2 (4)	NR	12	16.0 (14.4)	12.0 – 20.0	14 (28)	72 (11)	3 (3)
Hu, 2016 [74]	226	130 (58)	42 (14)	65 (29)	151 (67)	Grandchildren = 10 (4)	NR	22	37.1 (12.3)	35.5 – 38.7	85 (38)	66 (15)	NR
Hu, 2016 [73]	118	68 (58)	NR	34 (29)	79 (67)	Other relatives = 5 (4)	NR	22	37.6 (11.6)	35.5 – 39.7	43 (36)	NR	NR
Malik, 2013 [82]	51	42 (82)	66 (13)	38 (75)	8 (16)	Parent = 1 (2); friend = 1 (2); other relative = 3 (6)	NR	12	9.6 (9.0)	7.1 – 12.1	13 (25)	72 (10)	5 (4)
Trivedi, 2012 [113]	23	23 (100)	NR	23 (100)	0 (0)	0 (0)	NR	22	22.4 (15.4)	16.1 – 28.7	0 (0)	66 (7)	NR
HIV/AIDS													
Chandran, 2016 [57]	360	279 (78)	36 (10)	292 (81)	42 (12)	Parent = 20 (6); sibling = 6 (2)	NR	22	33.0 (17.9)	31.2 – 34.8	108 (30)	41 (11)	4 (2)
Huntington's disease													

Krch, 2008 [134]	17[dd]	9 (53)	NR	15 (88)	0 (0)	Parent = 2 (12)	3 (2)	22	32.5 (13.6)	26.0 – 39.0	9 (50)	NR	8 (NR)
Irritable bowel syndrome													
Wong, 2013 [117]	152	33 (22)	48 (16)	152 (100)	0 (0)	0 (0)	NR	22	22.1 (15.4)	19.7 – 24.5	119 (78)	NR	NR
Liver disease													
Bolden, 2010 [48]	73	57 (78)	48 (15)	NR	NR	NR	NR	22	21.5 (11.9)	18.8 – 24.2	38 (52)	51 (12)	NR
Multiple sclerosis													
Akkuş, 2011 [39]	49	31 (63)	42 (14)	27 (55)	6 (12)	Parent = 9 (18); other relative/NS = 7 (14)	96 (33)	22	36.4 (18.4)	31.2 – 41.6	NR	NR	NR
Bayen, 2015 [45]	96[ee]	48 (48)[ff]	52 (14)[gg]	69 (70)[hh]	3 (3)[ii]	Parent = 21 (21); sibling = 5 (5); friend = 1 (1)[jj]	NR	22	27.3 (19.9)	23.3 – 31.3	59 (64)[kk]	46 (14)	15 (10)
Buhse, 2015 [50]	102	34 (33)	61 (14)	87 (85)	5 (5)	Other relative = 5 (5); NS = 5 (5)	NR	22	36.5 (8.3)	34.9 – 38.1	NR	NR	NR
Ertekin, 2014 [61]	47	22 (47)	50 (12)	31 (66)	6 (13)	Parent = 10 (21)	NR	22	29.5 (12.5)	25.9 – 33.1	34 (72)	47 (11)	11 (6)
Özmen, 2018 [89]	92	60 (65)	NR	25 (27)	22 (24)	Parent = 29 (32); sibling = 16 (17)	NR	22	25.4 (9.5)	23.5 – 27.3	NR	NR	NR
Quig, 2007 [92]	1461	555 (38)	51 (NR)	1461 (100)	0 (0)	0 (0)	NR	22	22.9 (14.3)	22.2 – 23.6	NR	NR	NR
Rivera-Navarro, 2009 [93]	278	158 (57)	50 (13)	147 (53)	72 (26)	Parent = 35 (13); sibling = 13 (5); other relative = 7 (3); NS = 4 (1)	NR	22	22.0 (14.6)	20.3 – 23.7	183 (66)	43 (13)	11 (7)
Tzitzika, 2020 [121]	909	341 (38)	49 (27)	909 (100)	0 (0)	0 (0)	NR	22	49.6 (16.1)	48.6 – 50.6	NR	NR	NR
Myotonic dystrophy type 1													
Kurauchi, 2019 [128]	43	23 (53)	NR	18 (42)	2 (5)	Parent = 21 (49); sibling = 2 (5)	NR	22	20.7 (17.4)	15.5 – 25.9	22 (51)	45 (11)	NR
Parkinson's disease													
Bagheri, 2019 [125]	60	38 (63)	49 (13)	NR	NR	NR	NR	22	59.4 (18.0)	54.8 – 64.0	NR	NR	NR
Benavides, 2013 [46]	51	33 (65)	63 (14)	39 (76)	12 (24)	0 (0)	NR	22	26.7 (10.6)	23.8 – 29.6	22 (43)	68 (13)	8 (5)
Carod-Artal, 2013 [54]	50	44 (88)	56 (13)	39 (78)	7 (14)	Friend/other relative = 4 (8)	NR	22	20.2 (12.8)	16.7 – 23.7	10 (20)	65 (10)	9 (5)
Carrilho, 2018 [55]	21	17 (80)	53 (13)	10 (48)	8 (38)	Parent = 1 (5); daughter-in-law = 1 (5); grandchild = 1 (5)	43 (47)	22	28.4 (15.3)	21.9 – 34.9	5 (24)	68 (12)	12 (8)
Dorsey, 2011 [60]	27[ll]	17 (63)	65 (11)	NR	NR	NR	NR	22	13.6 (10.9)	9.5 – 17.7	11 (37)	69 (10)	NR
Grün, 2016 [66]	59	NR	64 (12)	NR	NR	NR	NR	22	25.8 (17.1)	21.4 – 30.2	NR	69 (10)	NR

Hagell, 2017 [68]	66	46 (70)	70 (8)	63 (95)	1 (2)	NS = 2 (3)	NR	22	28.3 (18.0)	24.0 – 32.6	21 (32)	72 (8)	9 (6)
Jones, 2017 [75]	51	33 (65)	66 (10)	47 (92)	0 (0)	Child/daughter-in-law/sibling/friend = 4 (8)	5 (14)	22	13.4 (12.2)	10.1 – 16.7	16 (31)	68 (8)	8 (4)
Leroi, 2012 [80]	28	28 (39)[mm]	63 (11)[nn]	38 (54)[oo]	33 (46)[pp]	0 (0)	NR	22	16.2 (11.0)	12.1 – 20.3	32 (45)[qq]	63 (9)	6 (5)
Martínez-Martín, 2007 [83]	72[rr]	62 (78)[ss]	61 (13)	61 (77)[tt]	15 (19)[uu]	NS = 3 (4)[vv]	27 (37)[ww]	22	26.5 (18.7)	22.2 – 30.8	28 (35)	69 (11)	8 (5)
Martínez-Martín, 2008 [84]	286[xx]	191 (67)	59 (14)	217 (76)	39 (14)	Friend/neighbor = 7 (2); other relative = 23 (8)	NR	22	18.1 (13.9)	16.5 – 19.7	134 (46)	65 (11)	8 (6)
Martínez-Martín, 2015 [85]	477[yy]	396 (70)[zz]	60 (14)[aaa]	349 (61)[bbb]	168 (29)[ccc]	NS = 53 (9)[ddd]	NR	22	19.2 (14.9)	17.9 – 20.5	239 (42)[eee]	71 (10)[fff]	8 (6)[ggg]
Ozdilek, 2012 [88]	50[hhh]	39 (78)	57 (13)	37 (74)	11 (22)	Sibling = 2 (4)	70 (NR)	22	27.6 (15.1)	23.4 – 31.8	16 (32)	68 (9)	10 (3)
Pomponi, 2016 [91]	28	15 (54)	69 (7)	28 (100)	0 (0)	0 (0)	NR	22	42.7 (13.3)	37.8 – 47.6	13 (46)	70 (5)	8 (5)
Rodríguez-Violante, 2015 [94]	201	147 (73)	52 (14)	107 (53)	61 (30)	Other relative = 33 (17)	NR	22	21.5 (16.3)	19.2 – 23.8	93 (46)	64 (13)	7 (6)
Santos-García, 2015 [96]	121	87 (72)	60 (15)	81 (67)	37 (31)	NS = 3 (2)	NR	22	16.0 (13.9)	13.5 – 18.5	51 (42)	71 (8)	7 (5)
Schiehser, 2013 [97]	51	41 (80)	67 (10)	47 (92)	0 (0)	NS = 4 (8)	NR	22	14.6 (13.7)	10.8 – 18.4	9 (18)	70 (8)	7 (4)
Schmotz, 2017 [98]	20	14 (70)	67 (11)	NR	NR	NR	NR	22	36.5 (15.3)	29.8 – 43.2	9 (45)	76 (6)	15 (8)
Shin, 2012 [102]	91	47 (51)[iii]	57 (10)	50 (55)	41 (45)	0 (0)	97 (45)	22	29.7 (19.5)	25.7 – 33.7	58 (64)	69 (8)	NR
Soulas, 2012 [104]	26	19 (73)	63 (9)	26 (100)	0 (0)	0 (0)	NR	22	28.2 (14.3)	22.7 – 33.7	7 (27)	64 (7)	16 (6)
Sturkenboom, 2013 [106]	40	29 (74)[jjj]	62 (14)	NR	NR	NR	NR	22	16.5 (12.4)	12.7 – 20.3	11 (28)	67 (11)	7 (6)
Tan, 2020 [131]	94	74 (79)	NR	44 (47)	38 (40)	Sibling = 4 (4); friend = 3 (3); NS = 5 (5)	NR	22	23.0 (13.2)	20.3 – 25.7	34 (36)	NR	7 (6)
Tessitore, 2018 [108]	126	88 (70)	58 (13)	76 (60)	40 (32)	Sibling = 4 (3); other relative = 6 (5)	NR	22	31.3 (15.9)	28.5 – 34.1	62 (49)	69 (8)	14 (5)
Tokunaga, 2009 [110]	54	39 (72)	62 (13)	33 (61)	15 (28)	Daughter-in-law/NS = 6 (11)	35 (43)	22	32.3 (14.9)	28.3 – 36.3	34 (63)	73 (6)	NR
Torny, 2018 [111]	38	32 (84)	68 (9)	38 (100)	0 (0)	0 (0)	NR	22	14.4 (12.7)	10.4 – 18.4	6 (16)	70 (8)	7 (6)
Yang, 2019 [122]	112	66 (59)	52 (13)	60 (54)	43 (38)	NS = 9 (8)	NR	22	19.6 (13.1)	17.2 – 22.0	46 (41)	65 (9)	NR
Progressive supranuclear palsy													
Schmotz, 2017 [98]	20	11 (55)	70 (9)	NR	NR	NR	NR	22	42.8 (8.7)	39.0 – 46.6	10 (50)	71 (6)	6 (3)

Rheumatoid arthritis													
Buitrago-Garcia, 2018 [135]	115	72 (63)	49 (18)	NR	NR	NR	NR	22	44.0 (14.0)	41.4 – 46.6	NR	NR	NR
Spinal cord injury													
Castellano-Tejedor, 2017 [56]	75	63 (84)	49 (13)	33 (44)	29 (39)	Parent= 4 (5); sibling = 6 (8); former partner = 1 (1); mother-in-law = 1 (1); uncle = 1 (1)	NR	22	42.4 (12.2)	39.6 – 45.2	NR	NR	NR
Coleman, 2015 [59]	40	35 (88)	44 (16)	NR	NR	NR	NR	22	26.7 (14.7)	22.1 – 31.3	NR	NR	NR
Ma, 2014 [81]	150	120 (80)	NR	117 (78)	0 (0)	NS = 33 (22)	NR	22	52.9 (11.6)	51.0 – 54.8	35 (23)	43 (12)	NR
Schulz, 2009 [99]	148[kkk]	131 (76)[lll]	53 (15)[mmm]	120 (70)[nnn]	14 (8)[ooo]	Parent = 4 (2); NS = 34 (20)[ppp]	NR	12	11.8 (7.8)	10.5 – 13.1	61 (35)	55 (13)	NR
Tough, 2017 [112]	118	86 (73)	51 (10)	118 (100)	0 (0)	0 (0)	14 (25)[qqq]	12	7.4 (7.2)	6.1 – 8.7	NR	NR	NR
Systemic sclerosis													
Cañedo-Ayala, 2020 [119]	202	79 (39)	57 (14)	146 (72)	24 (12)	Parent = 15 (7); sibling = 7 (4); friend = 7 (4); cousin = 1 (<1); neighbor = 1 (<1)	14 (13)	12	13.5 (9.8)	12.1 – 14.9	NR	58 (13)	NR
Transthyretin amyloidosis													
Stewart, 2018 [105]	32[rrr]	22 (69)	56 (13)	21 (72)[sss]	3 (10)[ttt]	Parent = 4 (14); NS = 1 (3)[uuu]	46 (50)	22	29.1 (14.7)	24.0 – 34.2	13 (22)	58 (12)	6 (4)

[a]NR = Not reported; [b]N = 200; [c]somewhat different means and standard deviations are calculated from pooling groups in Table 2, depending what groups are pooled – we used the first reported in the text (black/white); [d]care recipient data based on 104 patients; [e-i]N = 104; [j]care recipient data based on 27 patients; [k]care recipient data based on 231 patients; [l]N = 108; [m-o]N = 175; [p]time on dialysis; [q]care recipient data based on 25 patients; [r,s]N = 107; [t]N = 82; [u,v]N = 82; [w]somewhat different means and standard deviations are calculated from pooling groups in Table 2, depending what groups are pooled – we used the first reported in the table (male/female); [x,y]N = 375; [z]care recipient data based on 126 patients; [aa]N = 104; [bb]N = 108; [cc]N = 97; [dd]care recipient data based on 18 patients; [ee]care recipient data based on 99 patients; [ff-jj]N = 99; [kk]N = 92; [ll]care recipient data based on 30 patients; [mm-pp]N = 71; [qq]N = 71; [rr]care recipient data based on 80 patients; [ss-vv]N = 79; [ww]N = 56; [xx]care recipient data based on 289 patients; [yy]488 care recipients included without dementia; [zz]N = 562; [aaa]N = 584; [bbb-ddd]N = 570; [eee]N = 575; [fff,ggg]N = 584; [hhh]care recipient data based on 32 patients; [iii]N = 92; [jjj]N = 39; [kkk]care recipient data based on 173 patients; [lll,mmm]N = 173; [nnn-ppp]N = 172; [qqq]N = 106; [rrr]care recipient data based on 60 patients; [sss-uuu]N = 29

Table 2. Caregiver and care recipient variables among 12,397 informal caregivers

Caregiver Variables	**N (%) or mean (standard deviation)**	**Range of %s or means**	**Number of participants with data**
Female sex, *n (%),*	7,523 (62)	22-100	12,098
Age in years, *mean (standard deviation)*	53 (14)	36-71	9,655
Relation to care recipient, *n (%)*			11,983
Spouse or partner	8,203 (68)	0-100	
Child	2,091 (17)	0-100	
Parent	520 (4)	0-55	
Sibling	173 (1)	0-17	
Friend	42 (<1)	0-10	
Other[a]	954 (8)	0-100	
Years of caregiving, *mean (standard deviation)*	7 (6)	2-19	2,410
Hours of care per week, *mean (standard deviation)*	41 (30)	3-103	1,416

Care recipient variables			
Female sex, *n (%)*	3,708 (45)	0-78	8,264
Age in years, *mean (standard deviation)*	60 (11)	38-81	8,198
Years lived with the disease, *mean (standard deviation)*	9 (6)	1-42	4,959

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[a] Includes studies with combined relationship types (e.g., spouses and children = 100%). See table 1 for details.

Table 3. ZBI scores

Disease	**N studies**	**N participants**	**Pooled mean**[a]	**95% Confidence interval**	**I^2**
ZBI-22					
Celiac disease	1	94	17.5	14.9 to 20.1	
Myotonic dystrophy type 1	1	43	20.7	15.5 to 25.9	
Liver disease	1	73	21.5	18.8 to 24.2	
Irritable bowel syndrome	1	152	22.1	19.7 to 24.5	
Parkinson's disease	26	2,300	24.8	21.8 to 27.9	96.0%
Transthyretin amyloidosis	1	32	29.1	24.0 to 34.2	
Diabetes mellitus	1	228	29.2	27.1 to 31.3	
Amyotrophic lateral sclerosis	6	527	30.6	18.5 to 42.7	98.7%
Multiple sclerosis	8	3,034	31.2	22.0 to 40.4	99.6%
Epilepsy	3	550	31.3	18.0 to 44.6	98.1%
Huntington's disease	1	17	32.5	26.0 to 39.0	
HIV/AIDS	1	360	33.0	31.2 to 34.8	
Heart failure	7	841	34.2	24.6 to 43.7	99.4%
Chronic obstructive pulmonary disease	4	438	34.4	20.0 to 48.8	99.0%
Chronic kidney disease	18	2,050	35.4	29.7 to 41.1	99.2%
Spinal cord injury	3	265	40.8	27.8 to 53.8	98.4%
Progressive supranuclear palsy	1	20	42.8	39.0 to 46.6	
Rheumatoid arthritis	1	115	44.0	41.4 to 46.6	
Total	85	11,139	30.6	27.8 to 33.4	99.2%
ZBI-12					
Essential tremor	2	155	5.6	4.5 to 6.7	0%
Spinal cord injury	2	266	9.6	5.3 to 13.9	95.6%
Cirrhosis	2	190	12.9	10.5 to 15.4	76.5%
Amyotrophic lateral sclerosis	1	18	12.4	8.8 to 16.0	
Heart failure	3	200	12.6	9.5 to 15.7	77.2%
Systemic sclerosis	1	202	13.5	12.1 to 14.9	
Chronic kidney disease	1	88	14.4	12.5 to 16.3	
Diabetes mellitus	1	139	28.3	26.9 to 29.7	
Total	13	1,258	12.6	9.1 to 16.0	98.3%

[a] For disease groups with only one study, the mean ZBI score was reported as the pooled mean.

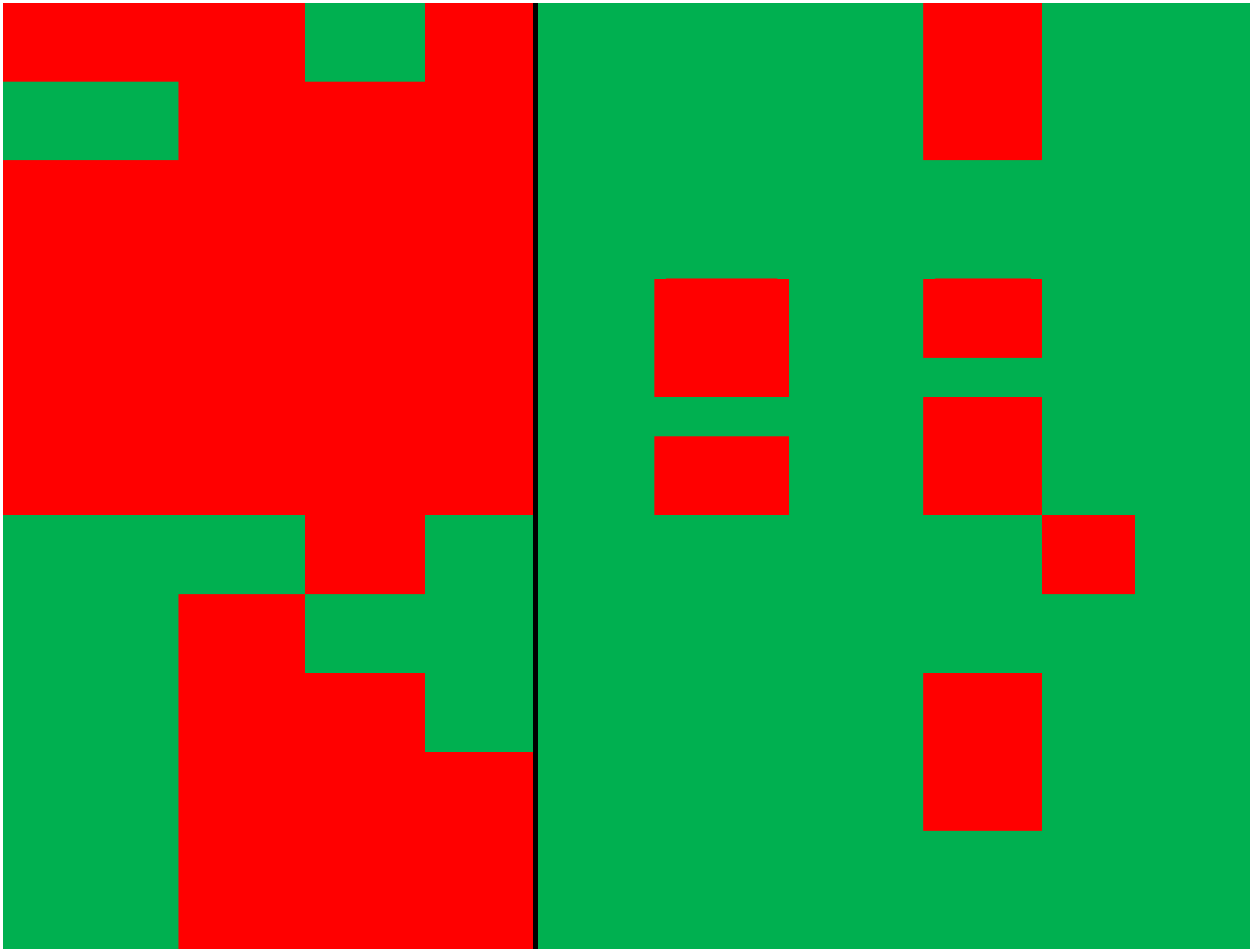
Table 4. Meta-regression analysis[a]

Variable	**Estimate**	**95% Confidence interval**
Caregiver age (years)	-0.07	-0.61 to 0.47
Percentage of female caregivers	0.02	-0.20 to 0.24
Percentage of caregivers as spouses/partners	-0.12	-0.29 to 0.06
Type of disease (reference group: neurological, N = 46)		
Organ failure (N = 29)	4.45	-3.25 to 12.15
Other (N = 10)	1.15	-8.29 to 10.59
Country's Human Development Index (reference group: very high, N = 65)		
High (N = 16)	7.31	-0.64 to 15.25
Medium (N = 4)	1.23	-14.11 to 16.57
Recruitment setting (reference group: outpatient, N = 46)		
Inpatient (N = 5)	5.93	-6.92 to 18.77
Community (N = 9)	10.19	0.13 to 20.25
Mixed (N = 6)	2.59	-10.25 to 15.42
Not reported (N = 19)	3.48	-3.46 to 10.42

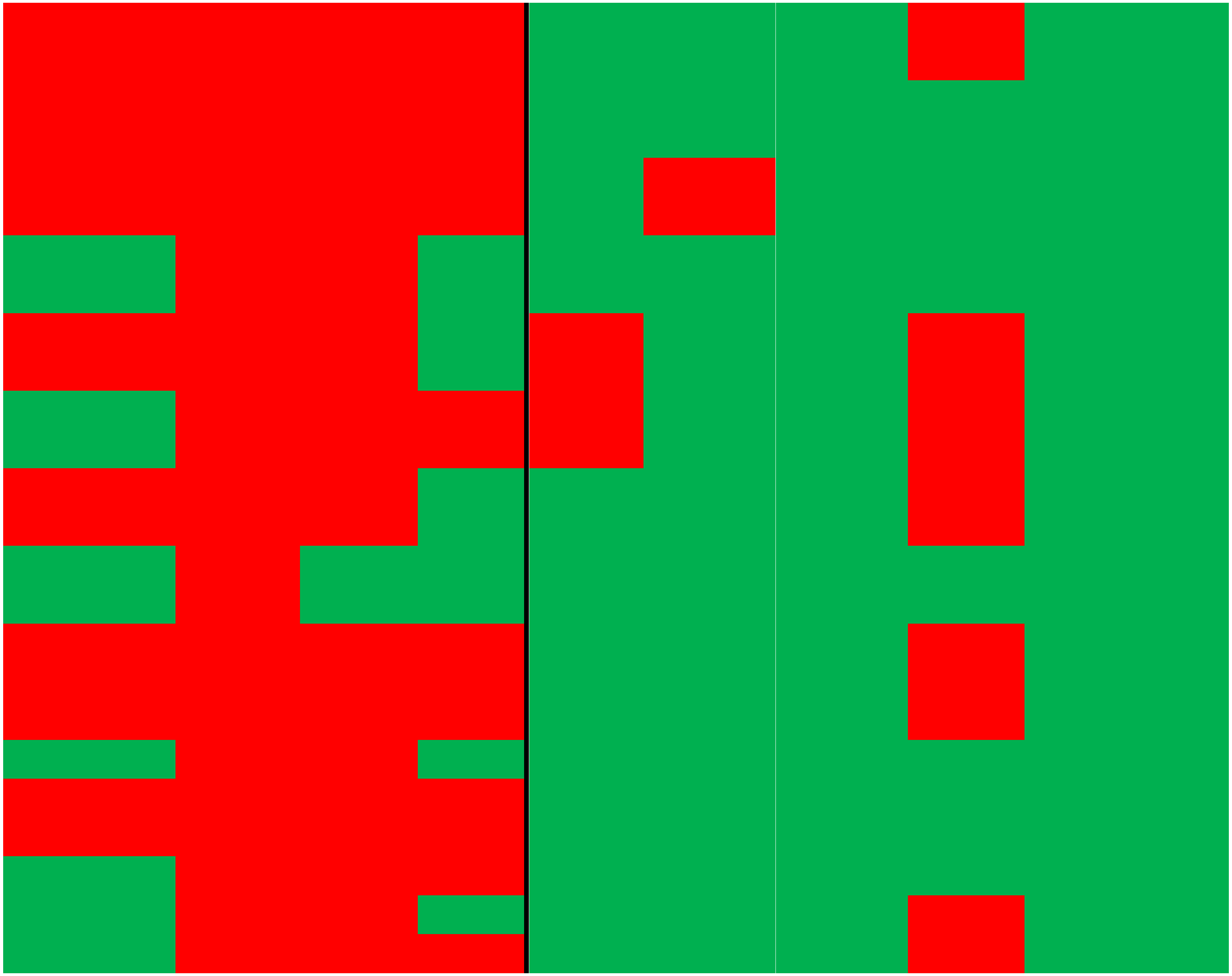
[a] Meta-regression model including all covariates at once, using multiple imputation by chained equations to account for missing data.

Table 5. Risk of bias among included studies

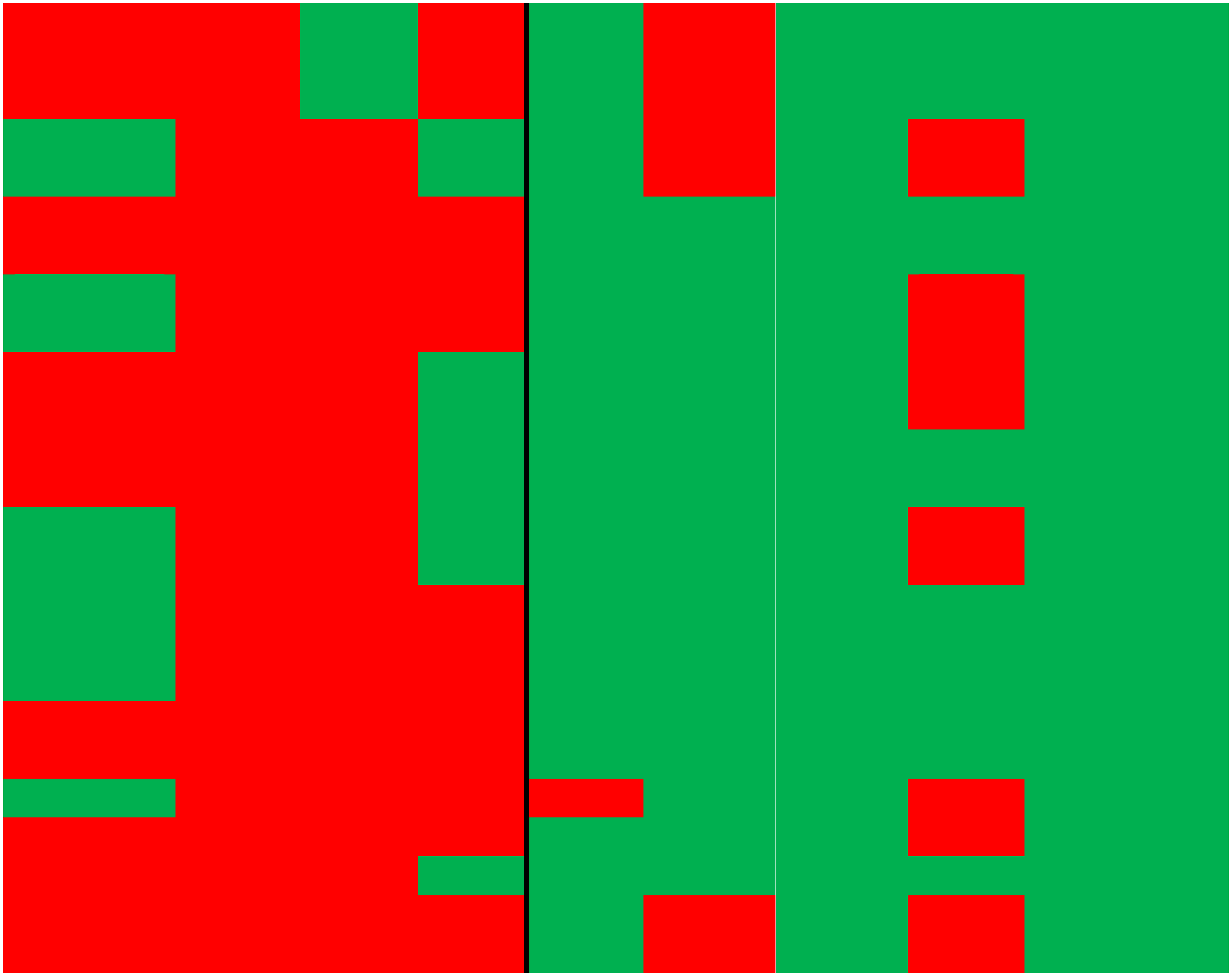
Study (First author, year)	**External validity**				**Internal validity**					
	Representative sample[a]	**Sampling frame**	**Random selection**	**Non-response bias**	**Direct data collection**	**Acceptable case definition**	**Study instrument**	**Mode of data collection**	**Time of data collection**	**Calculations**
Abed, 2020 [129]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Akkuş, 2011 [39]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Al Wakeel, 2016 [40]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Alvarez-Ude, 2004 [41]	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Badr, 2017 [42]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Bagheri, 2019 [125]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟥	🟩	🟩
Bajaj, 2011 [43]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Bañobre González, 2005 [44]	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Bayen, 2015 [45]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Benavides, 2013 [46]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩	🟩



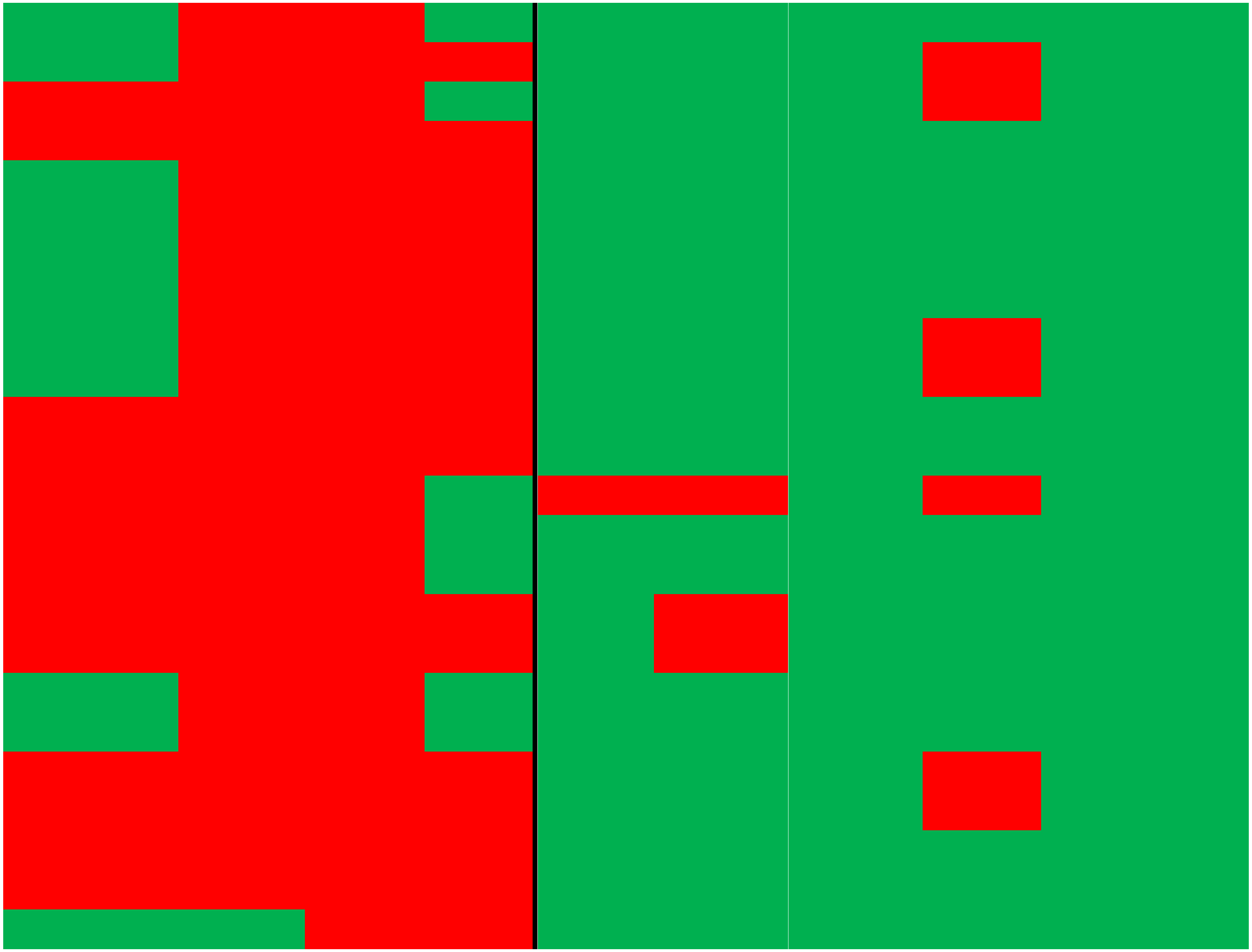
Bentley, 2014 [47]	🟥	🟥	🟩	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Bolden, 2010 [48]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Bozkurt Zincir, 2014 [49]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Buhse, 2015 [50]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Buitrago-Garcia, 2018 [135]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟥	🟩	🟩
Burke, 2018 [51]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟩	🟩	🟩
Cain, 2000 [52]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Çamur, 2020 [133]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟥	🟩	🟩
Cañedo-Ayala, 2020 [119]	🟩	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟥	🟩
Carmona Moriel, 2015 [53]	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Carod-Artal, 2013 [54]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩	🟩
Carrilho, 2018 [55]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Castellano-Tejedor, 2017 [56]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩



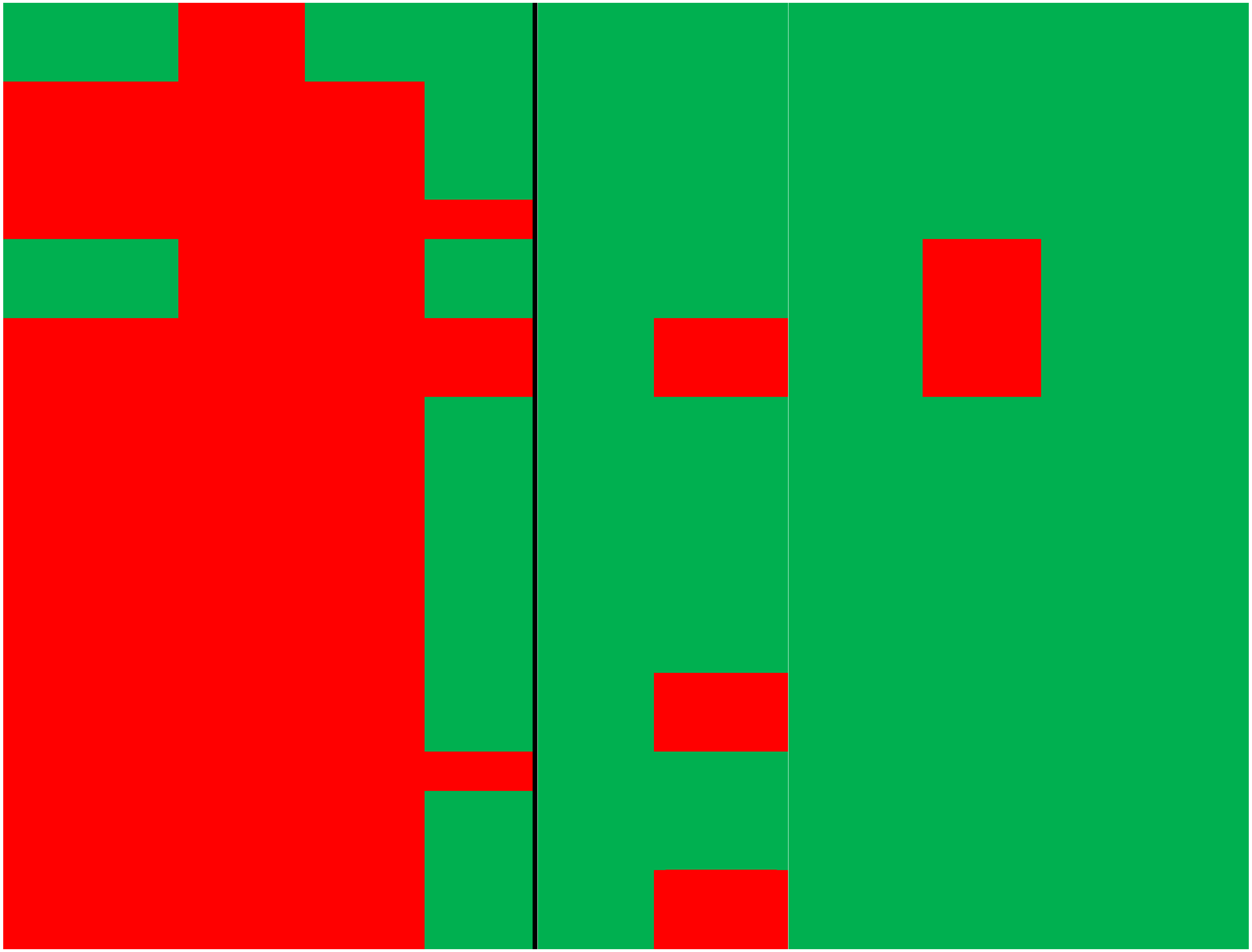
Cersonsky, 2019 [118]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Chandran, 2016 [57]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Chung, 2000 [58]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟩	🟩
Coleman, 2015 [59]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Dorsey, 2011 [60]	🟥	🟥	🟥	🟩	🟥	🟩	🟩	🟥	🟩
Ertekin, 2014 [61]	🟩	🟥	🟥	🟥	🟥	🟩	🟩	🟥	🟩
Etemadifar, 2014 [62]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Farzi, 2019 [126]	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Fernández-Garcia, 2020 [63]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Geng, 2017 [64]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Ghasemi, 2020 [127]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Göriş, 2016 [65]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Grün, 2016 [66]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Griva, 2016 [67]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩



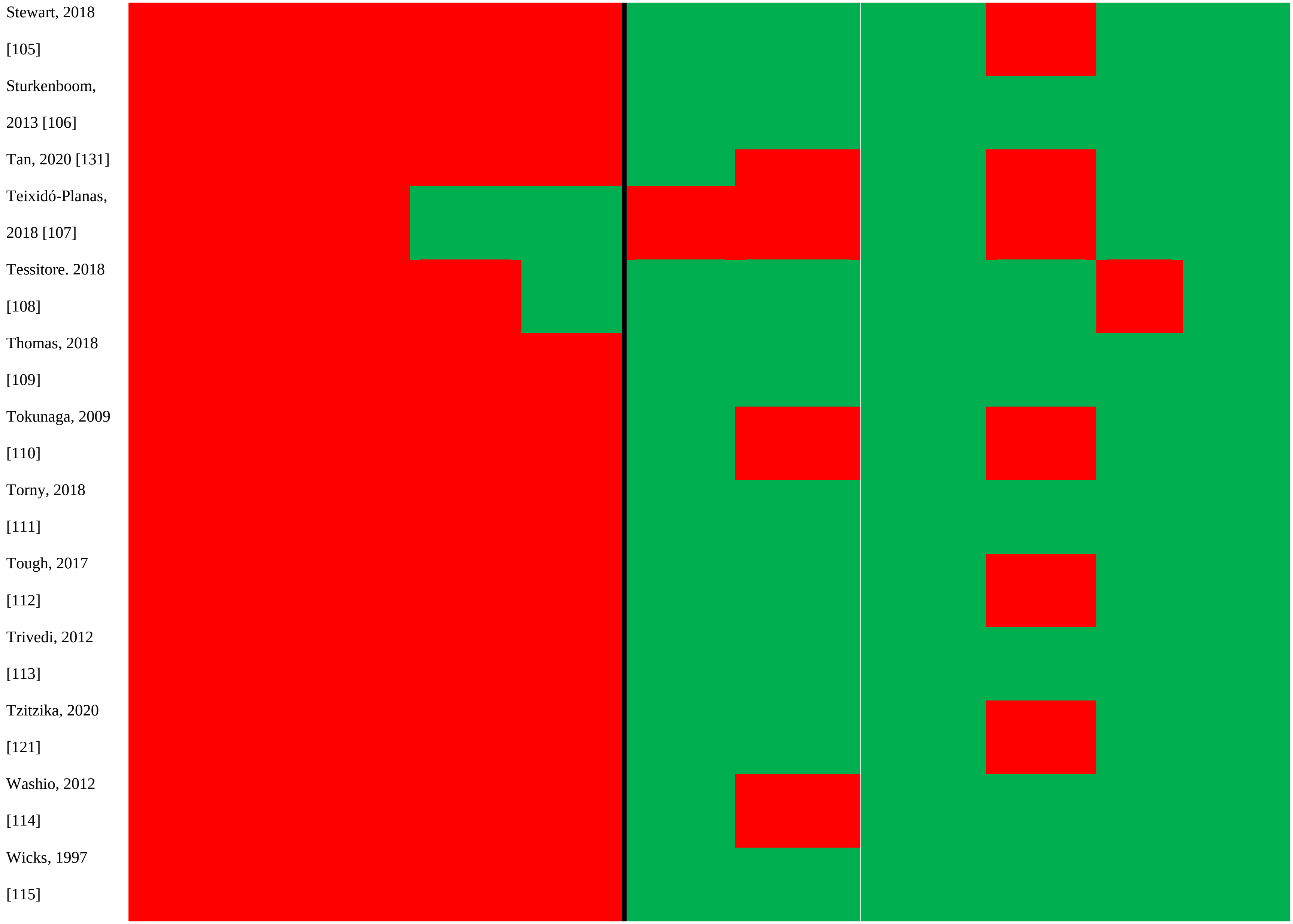
Hagell, 2017 [68]	🟥	🟥	🟩	🟥	🟩	🟥	🟩	🟩	🟩
Han, 2015 [69]	🟥	🟥	🟩	🟥	🟩	🟥	🟩	🟩	🟩
Hareendran, 2020 [124]	🟩	🟥	🟥	🟩	🟩	🟥	🟩	🟥	🟩
Hirakawa, 2008 [70]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Hoang, 2019 [132]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Hooker, 2018 [71]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Hooley, 2005 [72]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Hu, 2016 [73]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Hu, 2016 [74]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Jones, 2017 [75]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Karakis, 2014 [76]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Kellner, 2017 [77]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Kilic, 2017 [78]	🟩	🟥	🟥	🟥	🟥	🟩	🟩	🟥	🟩
Kim, 2011 [79]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Krch, 2009 [134]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Kurauchi, 2019 [128]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟥	🟩



Lai, 2019 [130]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Leroi, 2012 [80]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Ma, 2014 [81]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Malik, 2013 [82]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Martinez-Martin, 2007 [83]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Martinez-Martin, 2008 [84]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Martinez-Martin, 2015 [85]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Mollaoğlu, 2013 [86]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Oh, 2018 [87]	🟥	🟥	🟥	🟩	🟥	🟥	🟩	🟥	🟩
Ozdilek, 2012 [88]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Özmen, 2018 [89]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟩	🟩
Pagnini, 2010 [90]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Pashou, 2018 [120]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩
Pomponi, 2016 [91]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Quig, 2007 [92]	🟩	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟩



Rivera-Navarro, 2009 [93]	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Rodríguez-Violante, 2015 [94]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Roy, 2016 [95]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Santos-García, 2015 [96]	🟩	🟥	🟥	🟩	🟩	🟩	🟩	🟥	🟩
Schiehser, 2013 [97]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟥	🟩
Schmotz, 2017[b] [98]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Schmotz, 2017[c] [98]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Schulz, 2009 [99]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Shah, 2017 [100]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Shimoyama, 2003 [101]	🟥	🟥	🟥	🟩	🟩	🟥	🟩	🟩	🟩
Shin, 2012 [102]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩
Sotoudeh, 2019 [103]	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Soulas, 2012 [104]	🟥	🟥	🟥	🟩	🟩	🟥	🟩	🟩	🟩


Stewart, 2018 [105]
Sturkenboom, 2013 [106]
Tan, 2020 [131]
Teixidó-Planas, 2018 [107]
Tessitore. 2018 [108]
Thomas, 2018 [109]
Tokunaga, 2009 [110]
Torny, 2018 [111]
Tough, 2017 [112]
Trivedi, 2012 [113]
Tzitzika, 2020 [121]
Washio, 2012 [114]
Wicks, 1997 [115]

Wicks, 1998 [116]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Wong, 2013 [117]	🟥	🟥	🟥	🟥	🟩	🟥	🟩	🟩	🟩	🟩
Yang, 2019 [122]	🟩	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Zhang, 2020 [123]	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Total N high risk studies (%)	62 (63)	96 (98)	89 (91)	63 (64)	5 (5)	19 (19)	0 (0)	40 (41)	2 (2)	0 (0)

[a] See Supplemental Material 3 for specific items

[b] Patient sample: Parkinson's disease

[c] Patient sample: Progressive supranuclear palsy