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Risk Factors for Physical Disability in Patients With Leprosy
A Systematic Review and Meta-analysis

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IMPORTANCE The World Health Organization (WHO) 2016-2020 Global Leprosy Strategy aims to reinvigorate efforts to control leprosy and avert leprosy disability to less than 1 per million population.

OBJECTIVE To systematically identify clinical factors associated with physical disability in patients with leprosy.

DATA SOURCE Searches were conducted in Scopus, PubMed, and Web of Science databases to identify studies published from January 23, 1988, to May 23, 2018, using the keywords *leprosy* and *physical disability* and related terms.

STUDY SELECTION Studies that evaluated patients using the WHO leprosy disability grading system and reported the number of patients with and without disability by clinical characteristics were included.

DATA EXTRACTION AND SYNTHESIS The odds ratio (OR) was used as a measure of association between the clinical features and physical disability. Summary estimates were calculated using random-effects models.

MAIN OUTCOMES AND MEASURES The primary outcome was physical disability according to the WHO disability classification. The association between clinical features and physical disability was evaluated.

RESULTS The search identified 2447 reports. After screening titles and abstracts, 177 full-text articles were assessed for eligibility, and 32 studies were included in the systematic review; 24 of the 32 studies included sex information (39 571 patients), of whom 24 218 (61.2%) were male. Male patients with leprosy were more likely to have physical disability than female patients with leprosy (pooled OR, 1.66; 95% CI, 1.43-1.93; I^2, 81.3%; $P < .001$). Persons with multibacillary leprosy were 4-fold more likely to have physical disability than those with paucibacillary leprosy (pooled OR, 4.32; 95% CI, 3.37-5.53; I^2, 88.9%, $P < .001$). Patients having leprosy reactions were more likely to have disability (pooled OR, 2.43; 95% CI, 1.35-4.36; I^2, 92.1%; $P < .001$). Patients with lepromatous leprosy experienced 5- to 12-fold higher odds of disability.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis confirms the association between the presence of physical disabilities and male sex, multibacillary leprosy, leprosy reactions, and lepromatous presentation. These findings can guide the development of targeted interventions for early identification of individuals at greater risk of developing physical disabilities and education campaigns to promote early consultation to institute treatment for leprosy reactions and prevent physical disability.

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Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that affects the skin and peripheral nerves, leading to progressive physical disability and deformities if not diagnosed and treated early.[1-3] Despite a significant reduction in its global prevalence since the World Health Organization (WHO) implemented the free multidrug therapy program in 1995, leprosy remains a major cause of morbidity owing to its associated long-term disabilities and sequelae[4] in an estimated 2 million people worldwide.[5,6]

The WHO goal is to reduce leprosy disabilities to a target of less than 1 per million population through the strengthening of strategies for the prevention and reduction of deformities.[7] These strategies include the early recognition and prioritization of individuals with leprosy with characteristics associated with physical disability and the main focus of control programs and rehabilitation centers is to prevent and manage physical impairment to improve quality of life.[8,9] Although clinical features such as multibacillary (MB) leprosy and leprosy reactions are considered to predispose patients to physical disability and deformity,[2,5,10-13] there are no systematic analyses assessing the strength of this evidence. We report here a systematic review and meta-analysis to assess the clinical factors associated with physical disability in leprosy.

Key Points

Question What are the risk factors for physical disability in patients with leprosy?

Findings This systematic review and meta-analysis of 32 studies found a strong association between the presence of physical disabilities and male sex, multibacillary leprosy, leprosy reactions, and lepromatous presentation.

Meaning These findings can guide the early identification of individuals at higher risk of developing physical disabilities and the development of targeted preventive interventions.

Methods

This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline.[14] Institutional review board approval and informed consent were not required because all data were obtained from secondary data sources and data were deidentified.

Search Strategy and Selection Criteria

From April 4, 2018, to May 23, 2018, we systematically searched the PubMed, Scopus, and Web of Science databases to identify studies published from January 23, 1988, to May 23, 2018, using the keywords *leprosy* and *physical disability* and related terms, as described in eTable 1 in the Supplement. Two independent reviewers (H.L.de P. and C.D.F.de S.) screened the search results and identified potentially relevant studies based on their title and abstract. The studies were then read in full for consideration for inclusion in the analysis. Disagreements between the 2 reviewers were resolved by discussion. Studies were included if (1) patients had been assessed for physical disability using WHO leprosy disability grading[1]; (2) the study evaluated the association between the clinical presentation and physical disability; and (3) the clinical factors (exposure) were described according to the presence or absence of physical disability. We excluded publications without original data, such as reviews and opinions, those with overlapping data, and those from which data extraction was not possible. The authors of the latter studies were asked to provide access to the original databases, but none of them responded.

We considered age, sex, clinical presentation categories, the presence of leprosy reactions, and the WHO leprosy classification stage as exposure factors. The WHO classification includes paucibacillary leprosy (≤5 skin lesions, only 1 affected nerve trunk, or both; or negative findings on microscopy), MB leprosy (>5 skin lesions, more than 1 affected nerve trunk, or both; or positive findings on microscopy).[15] Clinical forms include tuberculoid, borderline, lepromatous, and indeterminate presentations.[16] Leprosy reactions include episodes characterized by the acute inflammation of skin lesions or nerves (type 1) and the appearance of inflamed cutaneous nodules with or without neuritis (type 2).[17]

Our primary outcome was physical disability according to the WHO disability classification.[1] In this classification, grade 0 indicates no sensory impairment or disability or damage to the eyes, hands, or feet; grade 1 indicates the presence of eye (visual acuity >6/60 in either eye) or sensory impairment in the hands or feet, without visible deformities or damages; and grade 2 indicates severe visual impairment (visual acuity <6/60 or inability to count fingers at 6 m) or the presence of visible deformity in the eyes (lagophthalmos, iridocyclitis, or corneal opacities) or visible deformity or damage on hands or feet (ie, ulcerations, traumatic injuries, resorption, claw, fallen hand, foot drop, or ankle contracture). We combined physical disability grades 1 and 2 and considered them jointly for statistical purposes.

Data Extraction and Bias Assessment

Data were extracted using standardized tables, including author, country, study design, participant characteristics, clinical setting (specialized health center [specializing in the care of patients with leprosy], general hospital [not specializing in the care of patients with leprosy], primary health care, or data obtained from a health information system) and physical disability (presence or absence). We extracted the number of patients with and without physical disability at the time of diagnosis and stratified for each exposure variable. Not all studies reported all variables and we used percentages to obtain the absolute number of patients by stratum.

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to grade the quality of each study. This tool is composed of 14 items that evaluate the representativeness and selection of the sample, description and measurement of exposure, follow-up of participants, and treatment of confounding. After critical appraisal of each item, the studies were rated as good, fair, or poor and the findings were discussed qualitatively. Disagreements were resolved by discussion.

Statistical Analysis

We calculated the pooled odds ratio (OR) for the primary outcome and forest plots to present results with 95% CIs. Not all studies reported data on all exposure variables, and the pooled OR was estimated from the data available for each variable. Pooled estimates were calculated using a random-effects model (DerSimonian and Laird method). Two-sided $P < .05$ was used to determine statistical significance. Statistical heterogeneity was assessed using the Cochran Q test[18] and quantified by the I^2 index.[19]

Subgroup analyses were performed according to the study design, population characteristics (adults, adults and children together, and children) and study setting. Publication bias was assessed by visually inspecting whether larger and smaller studies were asymmetrically distributed in the funnel plot.[20] Leave-1-out sensitivity analysis was conducted to examine the influence of each study on the pooled effect size.[21] Analyses were performed using Stata version 14.0 (StataCorp LP) and Review Manager, version 5.3 (Cochrane IMS) statistical software.

Results

The search strategy identified 2447 reports. After screening titles and abstracts, 177 full-text articles were assessed for eligibility and 32 were included in the analysis (eFigure 1 in the Supplement). The **Table** describes the characteristics of the studies included. Twenty-seven of the 32 studies (84%) were

Table. Characteristics of the Included Studies

Source	Country	Study Design	Population	Settings	Risk Factors Analyzed	Outcome	Sample Size	Total Disability
Zhanget et al,[22] 1993	China	Cross-sectional	Adults/children	Tertiary health center	Sex, WHO leprosy classification, clinical forms	Combined grades 1 and 2	14 257	8122
Tiendrebeogo et al,[23] 1996	Burkina Faso	Cross-sectional	Adults	Primary care	Sex, WHO leprosy classification	Combined grades 1 and 2	554	165
Çakiner et al,[24] 1997	Turkey	Cross-sectional	Adults	Hospital	Sex	Combined grades 1 and 2	711	546
Wittenhorst et al,[25] 1998	Zimbabwe	Surveillance	Adults/children	Information system	Sex, WHO leprosy classification	Grade 2	746	247
Croft et al,[26] 1999	Bangladesh	Cross-sectional	Adults/children	Tertiary health center	Sex, WHO leprosy classification	Combined grades 1 and 2	2664	415
Ahmad et al,[27] 2004	Pakistan	Cross-sectional	Adults	Hospital	Sex, WHO leprosy classification, clinical forms	Combined grades 1 and 2	100	41
Kar and Job,[11] 2005	India	Cross-sectional	Children	Tertiary health center	Sex, WHO leprosy classification, leprosy reaction	Grade 2	275	29
Rad et al,[28] 2007	Iran	Cross-sectional	Adults/children	Hospital	Sex, WHO leprosy classification	Combined grades 1 and 2	180	79
Silva-Sobrinho et al,[29] 2007	Brazil	Cross-sectional	Adults/children	Primary care	Sex	Combined grades 1 and 2	99	79
Lana et al,[30] 2008	Brazil	Surveillance	Adults/children	Information system	Sex, WHO leprosy classification	Combined grades 1 and 2	1461	672
Soomro et al,[31] 2008	Pakistan	Cross-sectional	Adults	Hospital	WHO leprosy classification	Separately grades 1 and 2	100	55
Ramos and Souto,[32] 2010	Brazil	Cross-sectional	Adults	Tertiary health center	Sex, WHO leprosy classification	Separately grades 1 and 2	193	51
El-Dawela et al,[33] 2012	Egypt	Cross-sectional	Adults/children	Hospital	WHO leprosy classification	Grade 2	587	204
Sarkar et al,[34] 2012	India	Cross-sectional	Adults	Hospital	WHO leprosy classification	Separately grades 1 and 2	244	244
Kumar et al,[10] 2012	India	Cohort	Adults/children	Tertiary health center	Sex, WHO leprosy classification, clinical forms	Grade 2	293	27
Nardi et al,[35] 2012	Brazil	Cross-sectional	Adults/children	Primary care	Sex, WHO leprosy classification, clinical forms	Separately grades 1 and 2	335	71
van Brakel et al,[5] 2012	Indonesia	Cross-sectional	Adults	Primary care	Sex, WHO leprosy classification	Separately grades 1 and 2	1308	1003
Monteiro et al,[36] 2013	Brazil	Cross-sectional	Adults/children	Primary care	WHO leprosy classification, leprosy reaction	Separately grades 1 and 2	282	44
Oliveira et al,[37] 2013	Brazil	Cross-sectional	Adults/children	Tertiary health center	Sex	Separately grades 1 and 2	494	142
Guerrero et al,[38] 2013	Colombia	Cross-sectional	Adults/children	Primary care	Sex, WHO leprosy classification	Combined grades 1 and 2	333	117
de Castro et al,[39] 2014	Brazil	Cross-sectional	Adults	Primary care	Sex, WHO leprosy classification	Combined grades 1 and 2	225	137
Silva et al,[40] 2015	Brazil	Cross-sectional	Adults/children	Primary care	Sex, WHO leprosy classification	Grade 2	1916	366
Monteiro et al,[41] 2015	Brazil	Surveillance	Adults/children	Information system	Sex, WHO leprosy classification, leprosy reaction, clinical forms	Grade 2	12 328	664
Santos et al,[2] 2015	Brazil	Surveillance	Adults/children	Information system	Sex, WHO leprosy classification, leprosy reaction, clinical forms	Combined grades 1 and 2	2358	656

(continued)

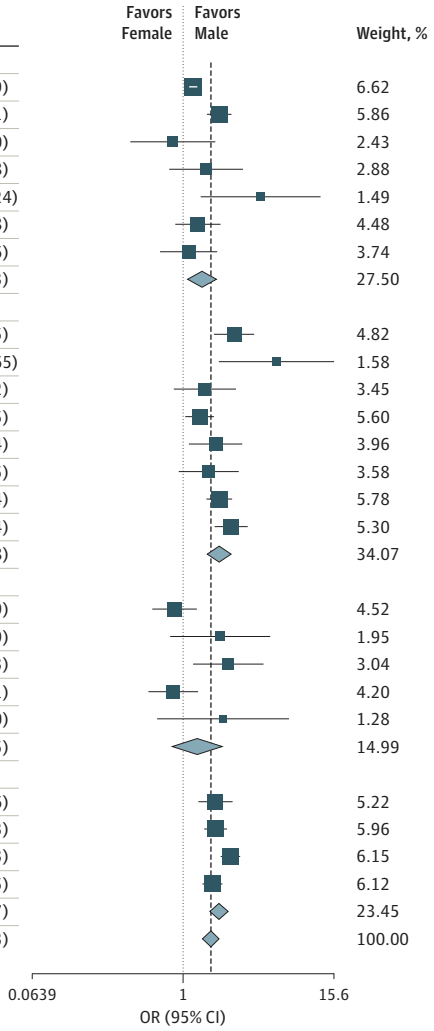
Table. Characteristics of the Included Studies (continued)

Source	Country	Study Design	Population	Settings	Risk Factors Analyzed	Outcome	Sample Size	Total Disability
Sethi and Rao,[42] 2015	India	Cross-sectional	Children	Hospital	WHO leprosy classification, clinical forms	Separately grades 1 and 2	94	32
Patel and Modi,[43] 2016	India	Cross-sectional	Adults	Tertiary health center	Sex, WHO leprosy classification, leprosy reaction	Separately grades 1 and 2	239	127
Onyeonoro et al,[44] 2016	India	Cross-sectional	Adults/children	Hospital	Sex, WHO leprosy classification	Separately grades 1 and 2	287	168
Queirós et al,[45] 2016	Brazil	Cross-sectional	Adults/children	Hospital	WHO leprosy classification	Separately grades 1 and 2	458	63
Anjum et al,[46] 2017	India	Cross-sectional	Adults/children	Tertiary health center	WHO leprosy classification	Combined grades 1 and 2	54	48
Rodrigues et al,[13] 2017	Brazil	Cross-sectional	Adults/children	Hospital	Sex, WHO leprosy classification	Combined grades 1 and 2	182	124
Darlong et al,[47] 2017	India	Cross-sectional	Children	Hospital	WHO leprosy classification	Grade 2	319	21
Haefner et al,[12] 2017	Brazil	Cross-sectional	Adults/children	Primary care	Sex	Separately grades 1 and 2	910	262

Abbreviation: WHO, World Health Organization.

Figure 1. Subgroup Analysis for Sex by Location of Enrollment

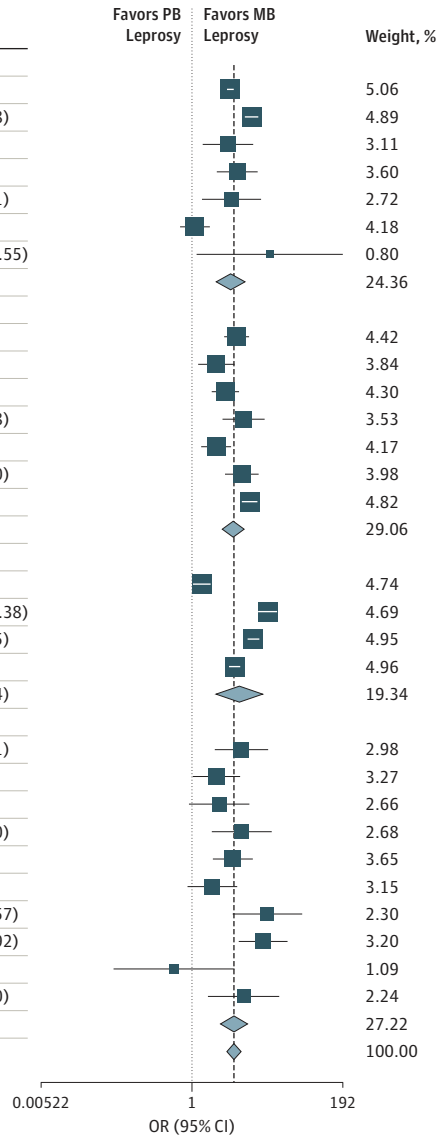
Study	Male No. of Events	Male Total Participants	Female No. of Events	Female Total Participants	OR (95% CI)	Weight, %
Specialized health center						
Zhang et al,[22] 1993	6028	10356	2094	3901	1.20 (1.12-1.29)	6.62
Croft et al,[26] 1999	285	1481	130	1183	1.93 (1.54-2.41)	5.86
Kar and Job,[11] 2005	16	163	13	112	0.83 (0.38-1.80)	2.43
Ramos and Souto,[32] 2010	32	94	19	75	1.52 (0.78-2.98)	2.88
Kumar et al,[10] 2012	23	163	4	104	4.11 (1.38-12.24)	1.49
Oliveira et al,[37] 2013	78	200	64	195	1.31 (0.87-1.98)	4.48
Patel and Modi,[43] 2016	79	146	48	93	1.11 (0.66-1.86)	3.74
Subtotal I^2 = 72.4%; P = .001	6541	12603	2372	5663	1.41 (1.08-1.83)	27.50
Primary health care						
Tiendrebeogo et al,[23] 1996	93	240	72	360	2.53 (1.75-3.65)	4.82
Silva-Sobrinho et al,[29] 2007	59	66	20	33	5.48 (1.92-15.65)	1.58
Nardi et al,[35] 2012	39	107	32	115	1.49 (0.84-2.62)	3.45
van Brakel et al,[5] 2012	647	822	356	486	1.35 (1.04-1.75)	5.60
Guerrero et al,[38] 2013	84	208	33	121	1.81 (1.11-2.94)	3.96
de Castro et al,[39] 2014	67	100	70	125	1.60 (0.92-2.75)	3.58
Silva et al,[40] 2015	224	863	142	925	1.93 (1.53-2.44)	5.78
Haefner et al,[12] 2017	177	478	85	432	2.40 (1.78-3.24)	5.30
Subtotal I^2 = 57.1%; P = .02	1390	2884	810	2597	1.93 (1.56-2.38)	34.07
General hospital						
Çakiner et al,[24] 1997	401	527	145	184	0.86 (0.57-1.29)	4.52
Ahmad et al,[27] 2004	32	70	9	30	1.96 (0.79-4.89)	1.95
Rad et al,[28] 2007	59	116	20	64	2.28 (1.20-4.33)	3.04
Onyeonoro et al,[44] 2016	88	167	80	140	0.84 (0.53-1.31)	4.20
Rodrigues et al,[13] 2017	74	79	50	57	2.07 (0.62-6.90)	1.28
Subtotal I^2 = 61.7%; P = .03	654	959	304	475	1.29 (0.82-2.05)	14.99
Health information system						
Wittenhorst et al,[25] 1998	155	396	92	350	1.80 (1.32-2.46)	5.22
Lana et al,[30] 2008	397	745	275	711	1.81 (1.47-2.23)	5.96
Monteiro et al,[41] 2015	490	5469	174	4361	2.37 (1.98-2.83)	6.15
Santos et al,[2] 2015	386	1162	270	1196	1.71 (1.42-2.05)	6.12
Subtotal I^2 = 59.5%; P = .06	1428	7772	811	6618	1.92 (1.63-2.27)	23.45
Overall I^2 = 81.3%; P < .001	10013	24218	4297	15353	1.66 (1.43-1.93)	100.00



Square data markers represent odds ratio, with size representing the statistical weight of the study using random-effects analysis. Error bars represent 95% CI. Diamond data marker represents the overall OR and 95% CI for the outcome of interest.

Figure 2. Subgroup Analysis for World Health Organization (WHO) Leprosy Classification by Location of Enrollment

Study	MB Leprosy No. of Events	MB Leprosy Total Participants	PB Leprosy No. of Events	PB Leprosy Total Participants	OR (95% CI)	Weight, %
Specialized health center						
Zhang et al,[22] 1993	1610	1984	6501	12256	3.81 (3.39-4.29)	5.06
Croft et al,[26] 1999	203	444	212	2220	7.98 (6.31-10.08)	4.89
Kar and Job,[11] 2005	9	37	20	238	3.50 (1.45-8.44)	3.11
Ramos and Souto,[32] 2010	34	70	16	98	4.84 (2.38-9.86)	3.60
Kumar et al,[10] 2012	17	125	5	131	3.97 (1.42-11.11)	2.72
Patel and Modi,[43] 2016	78	144	49	95	1.11 (0.66-1.86)	4.18
Anjum et al,[46] 2017	45	51	1	3	15.00 (1.17-191.55)	0.80
Subtotal I^2 = 89.8%; P <.001	1996	2855	6804	15041	3.85 (2.31-6.42)	24.36
Primary health care						
Tiendrebeogo et al,[23] 1996	66	114	99	440	4.74 (3.07-7.31)	4.42
Nardi et al,[35] 2012	54	141	17	81	2.34 (1.24-4.40)	3.84
van Brakel et al,[5] 2012	572	886	29	80	3.20 (1.99-5.16)	4.30
Monteiro et al,[36] 2013	33	112	11	170	6.04 (2.90-12.58)	3.53
Guerrero et al,[38] 2013	92	222	25	107	2.32 (1.38-3.91)	4.17
de Castro et al,[39] 2014	98	125	39	100	5.68 (3.16-10.20)	3.98
Silva et al,[40] 2015	286	747	80	1041	7.45 (5.68-9.78)	4.82
Subtotal I^2 = 76.9%; P <.001	1201	2347	300	2019	4.21 (2.87-6.17)	29.06
Health information system						
Wittenhorst et al,[25] 1998	138	377	107	368	1.41 (1.04-1.92)	4.74
Lana et al,[30] 2008	626	1013	46	442	13.93 (10.01-19.38)	4.69
Monteiro et al,[41] 2015	547	3794	117	6035	8.52 (6.95-10.45)	4.95
Santos et al,[2] 2015	462	1058	194	1300	4.42 (3.64-5.37)	4.96
Subtotal I^2 = 97.7%; P <.001	1773	6242	464	8145	5.21 (2.32-11.74)	19.34
General hospital						
Ahmad et al,[27] 2004	33	58	8	42	5.61 (2.22-14.21)	2.98
Rad et al,[28] 2007	111	126	41	54	2.35 (1.03-5.35)	3.27
Soomro et al,[31] 2008	14	52	6	48	2.58 (0.90-7.39)	2.66
El-Dawela et al,[33] 2012	200	544	4	43	5.67 (2.00-16.10)	2.68
Sarkar et al,[34] 2012	36	114	13	130	4.15 (2.07-8.33)	3.65
Sethi and Rao,[42] 2015	18	42	14	52	2.04 (0.86-4.84)	3.15
Onyeonoro et al,[44] 2016	145	253	3	34	13.87 (4.13-46.57)	2.30
Queirós et al,[45] 2016	97	311	6	164	11.94 (5.10-27.92)	3.20
Rodrigues et al,[13] 2017	106	117	18	19	0.54 (0.07-4.40)	1.09
Darlong et al,[47] 2017	18	177	3	163	6.04 (1.74-20.90)	2.24
Subtotal I^2 = 59.5%; P = .02	778	1794	116	749	4.33 (2.69-6.95)	27.22
Overall I^2 = 88.9%; P <.001	5748	13238	7684	25954	4.32 (3.37-5.53)	100.00



Square data markers represent odds ratio, with size representing the statistical weight of the study using random-effects analysis. Error bars represent 95% CI. Diamond data marker represents the overall OR and 95% CI for the outcome of interest. MB indicates multibacillary; PB, paucibacillary.

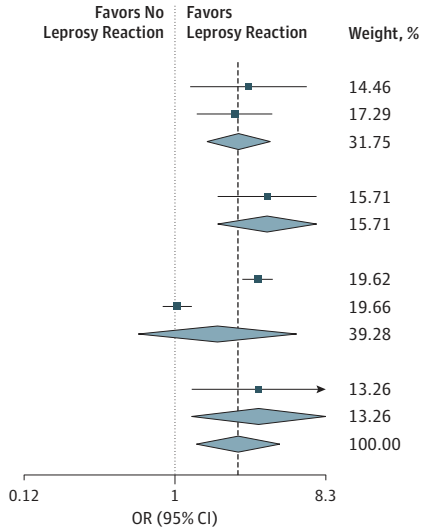
cross-sectional, 4 (13%) were from surveillance systems (continuous and routine reporting of cases for monitoring purposes) and 1 (3%) was a cohort study. Nine (28%) studies included adults, 3 (9%) included children, and 20 (63%) enrolled both adults and children and reported combined findings. Eleven (34%) studies were based in general hospitals, 9 (28%) in primary health care settings and 8 (25%) in specialized health care centers, and 4 (13%) were data extracted from health information systems of leprosy control programs, the last of which came from the systematic collection of surveillance services. The racial/ethnic origin of the patients was not reported.

The risk of bias of the studies is showed in eTable 2 in the Supplement. All studies had clear objectives and eligibility criteria, recruited subjects from the same population, and described the definitions of exposure factors and outcomes. However, 28 of the 32 studies did not report the number of eligible participants recruited into the study. Because 27 of the 32 studies were cross-sectional, the exposure and outcome status (physical disability) of the participants were collected at the same time, introducing potential sources of bias.

Twenty-four of the 32 studies had sex information (39 571 patients), of whom 24 218 (61.2%) were male.[2,5,10-13,22-30,32,35,37-41,43] Male patients were more likely to have physical disability than female patients (pooled OR, 1.66; 95% CI, 1.43-1.93; I^2, 81.3%; P < .001) and the odds of physical disability did not depend on the study location (**Figure 1** and eFigure 2 in the Supplement).[2,5,10-13,22-30,32,35,37-41,43,44]

Figure 3. Subgroup Analysis for Leprosy Reaction by Location of Enrollment

Study	Leprosy Reaction No. of Events	Leprosy Reaction Total Participants	No Leprosy Reaction No. of Events	No Leprosy Reaction Total Participants	OR (95% CI)
Specialized health center					
Kar and Job,[11] 2005	11	55	18	220	2.81 (1.24-6.36)
Patel and Modi,[43] 2016	65	100	62	139	2.31 (1.36-3.92)
Subtotal I^2 = 0.0%; P = .69	76	155	80	359	2.44 (1.57-3.81)
Primary health care					
Monteiro et al,[36] 2013	18	56	26	226	3.64 (1.82-7.29)
Subtotal	18	56	26	226	3.64 (1.82-7.29)
Health information system					
Monteiro et al,[41] 2015	140	802	330	5301	3.19 (2.57-3.94)
Santos et al,[2] 2015	162	655	493	2043	1.03 (0.84-1.27)
Subtotal I^2 = 98.2%; P <.001	302	1457	823	7344	1.81 (0.60-5.52)
General hospital					
Sethi and Rao,[42] 2015	14	26	18	68	3.24 (1.27-8.30)
Subtotal	14	26	18	68	3.24 (1.27-8.30)
Overall I^2 = 92.1%; P <.001	410	1694	947	7997	2.43 (1.35-4.36)



Square data markers represent odds ratio (OR), with size representing the statistical weight of the study using random-effects analysis. Error bars represent 95% CI. Diamond data marker represents the overall OR and 95% CI for the outcome of interest.

World Health Organization leprosy classification data were obtained from 28 studies including 39 192 patients.[2,5,10,11,13,22,23,25-28,30-39,41-47] Paucibacillary leprosy was more frequent than MB leprosy (25 954 [66.2%] vs 13 238 [33.8%], respectively), but patients with MB leprosy were 4-fold more likely to have physical disabilities (pooled OR, 4.32; 95% CI, 3.37-5.53; I^2, 88.9%, P < .001) independent of the study location (**Figure 2** and eFigure 3 in the Supplement).[2,5,10,11,22,23,25,27,28,30-36,38-47]

Six studies reported leprosy reactions and disability,[2,11,36,41-43] including 9691 patients, of whom 1694 (17.5%) had leprosy reactions and 7997 (82.5%) had no reaction, resulting in a pooled OR of 2.43 (95% CI, 1.35-4.36; I^2, 92.1%; P < .001) (**Figure 3** and eFigure 4 in the Supplement).[2,11,36,41-43] The clinical presentation was reported in 7 studies. Patients with lepromatous forms were more likely to have disability than patients with borderline forms (pooled OR, 2.94; 95% CI, 1.72-5.02; I^2, 92.2%; P < .001), tuberculoid (pooled OR, 5.85; 95% CI, 3.56-9.61; I^2, 90.8%; P < .001), or indeterminate leprosy (pooled OR, 12.53; 95% CI, 6.34-24.76; I^2, 86.4%; P < .001) and these pooled ORs were not dependent on the study location (**Figure 4** and eFigures 5-7 in the Supplement).[2,22,27,35,42]

Leave-1-out sensitivity analysis was conducted by means of omitting 1 study at a time and examining the influence of each study on the pooled effect size. Sensitivity analysis showed that the result was robust. No evidence of publication bias was observed (eFigures 8-12 in the Supplement).

Discussion

Factors predisposing to the development of physical disability in leprosy have been reported extensively, providing an excellent opportunity for a comprehensive analysis. This review confirms that male patients, those with MB leprosy, leprosy reactions, and lepromatous presentations are more likely to have physical disabilities.

Male patients were almost 2 times more likely than female patients to have physical disability. This sex difference has been attributed to social behaviors and reluctance and difficulties in accessing health services.[48] Men often ignore leprosy symptoms and seek health services at more advanced stages of the disease and with more severe clinical manifestations.[49-51] Health professionals should be aware of men's increased risk of physical disability during active case finding activities and contact tracing, to ensure that male contacts and secondary cases are not missed during home visits.

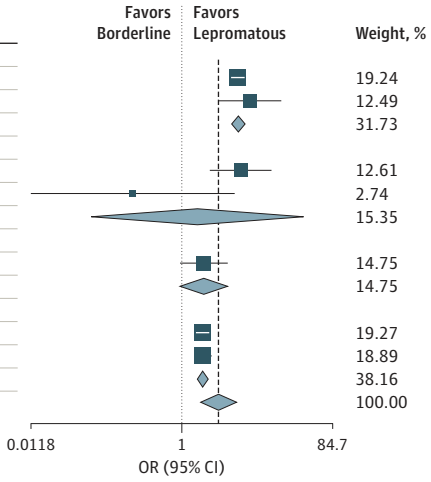
Leprosy disease progression is determined by the cellular immune responses to *M leprae*, which are expressed through different pathophysiologic mechanisms. The absence of cellular and enhanced humoral immune responses in patients with MB leprosy is associated with high bacilli loads and with development of neuritis and peripheral nerve damage.[26,52] Patients with MB leprosy in the present systematic review and meta-analysis were more likely to have physical disabilities, highlighting the importance of good clinical classification and microscopic detection of bacilli.[16]

Although tuberculoid and indeterminate leprosy are the most frequent clinical presentations, our meta-analysis demonstrates that patients with lepromatous leprosy have 5- to 12-fold greater odds of disability. Lepromatous leprosy is characterized by helper T-cell 2 immune responses with increased production of interleukin 4 and interleukin 10 and activation of regulatory T cells, a robust but ineffective production of antibodies with formation of immune complexes, and a failure to restrict *M leprae* growth, especially into the Schwann cells.[53] The immunologic response to infected Schwann cells is associated with nerve injuries and physical disability.[54]

Figure 4. Forest Plot Showing the Pooled Odds Ratio (OR) for Physical Disability in Patients With Leprosy by Clinical Form

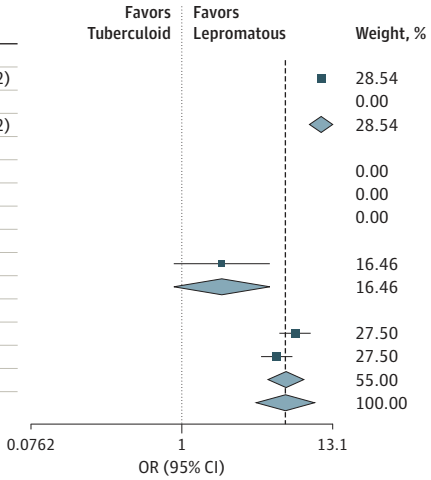
A Lepromatous and borderline forms

Study	Lepromatous No. of Events	Lepromatous Total Participants	Borderline No. of Events	Borderline Total Participants	OR (95% CI)	Weight, %
Specialized health center						
Zhang et al,[22] 1993	950	1066	3689	6032	5.20 (4.26-6.35)	19.24
Kumar et al,[10] 2012	13	51	9	205	7.45 (2.97-18.66)	12.49
Subtotal I^2 = 0.0%; P = .45	963	1117	3698	6237	5.29 (4.35-6.43)	31.73
General hospital						
Ahmad et al,[27] 2004	24	35	17	61	5.65 (2.28-13.99)	12.61
Sethi and Rao,[42] 2015	0	3	30	80	0.24 (0.01-4.74)	2.74
Subtotal I^2 = 75.9%; P = .04	24	38	47	141	1.59 (0.07-36.24)	15.35
Primary health care						
Nardi et al,[35] 2012	25	52	29	89	1.92 (0.95-3.86)	14.75
Subtotal	25	52	29	89	1.92 (0.95-3.86)	14.75
Health information system						
Monteiro et al,[41] 2015	201	977	309	2509	1.84 (1.52-2.24)	19.27
Santos et al,[2] 2015	243	476	170	473	1.86 (1.43-2.41)	18.89
Subtotal I^2 = 0.0%; P = .96	444	1453	479	2982	1.85 (1.58-2.16)	38.16
Overall I^2 = 92.2%; P < .001	1456	2660	4253	9449	2.94 (1.72-5.02)	100.00



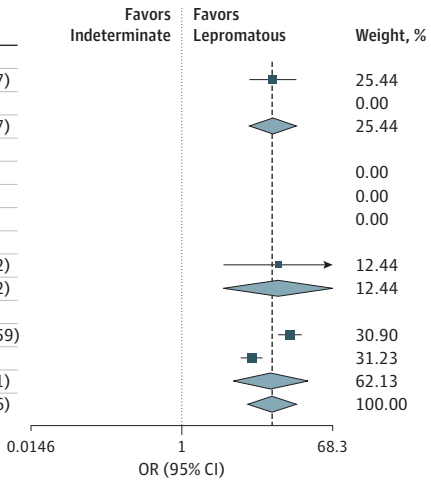
B Lepromatous and tuberculoid forms

Study	Lepromatous No. of Events	Lepromatous Total Participants	Tuberculoid No. of Events	Tuberculoid Total Participants	OR (95% CI)	Weight, %
Specialized health center						
Zhang et al,[22] 1993	950	1066	3456	8000	10.77 (8.84-13.12)	28.54
Kumar et al,[10] 2012	13	51	0	0	(Excluded)	0.00
Subtotal	963	1117	3456	8000	10.77 (8.84-13.12)	28.54
General hospital						
Ahmad et al,[27] 2004					(Excluded)	0.00
Sethi and Rao,[42] 2015	0	3	0	1	(Excluded)	0.00
Subtotal	24	38	0	1		0.00
Primary health care						
Nardi et al,[35] 2012	25	52	15	47	1.98 (0.87-4.48)	16.46
Subtotal	25	52	15	47	1.98 (0.87-4.48)	16.46
Health information system						
Monteiro et al,[41] 2015	201	977	84	2320	6.89 (5.28-9.01)	27.50
Santos et al,[2] 2015	243	476	118	689	5.05 (3.86-6.59)	27.50
Subtotal I^2 = 61.8%; P = .11	444	1453	202	3009	5.90 (4.34-8.01)	55.00
Overall I^2 = 90.8%; P < .001	1456	2660	3673	11057	5.85 (3.56-9.61)	100.00



C Lepromatous and indeterminate forms

Study	Lepromatous No. of Events	Lepromatous Total Participants	Indeterminate No. of Events	Indeterminate Total Participants	OR (95% CI)	Weight, %
Specialized health center						
Zhang et al,[22] 1993	950	1066	16	41	12.80 (6.64-24.67)	25.44
Kumar et al,[10] 2012	13	51	0	0	(Excluded)	0.00
Subtotal	963	1117	16	41	12.80 (6.64-24.67)	25.44
General hospital						
Ahmad et al,[27] 2004					(Excluded)	0.00
Sethi and Rao,[42] 2015	0	3	0	1	(Excluded)	0.00
Subtotal	24	38	0	1		0.00
Primary health care						
Nardi et al,[35] 2012	25	52	2	34	14.81 (3.21-68.32)	12.44
Subtotal	25	52	2	34	14.81 (3.21-68.32)	12.44
Health information system						
Monteiro et al,[41] 2015	201	977	46	3698	20.56 (14.79-28.59)	30.90
Santos et al,[2] 2015	243	476	73	567	7.06 (5.21-9.57)	31.23
Subtotal I^2 = 95.4%; P = .001	444	1453	119	4265	12.02 (4.21-34.31)	62.13
Overall I^2 = 86.4%; P = .001	1456	2660	137	4341	12.53 (6.34-24.76)	100.00



A, Subgroup analysis for lepromatous and borderline forms. B, Subgroup analysis for lepromatous and tuberculoid forms. C, Subgroup analysis for lepromatous and indeterminate forms. Square data markers represent odds ratio, with size representing the statistical weight of the study using random-effects analysis. Error bars represent 95% CI. Diamond data marker represents the overall OR and 95% CI for the outcome of interest.

Individuals with leprosy reactions are more susceptible to peripheral nerve injuries and sequelae. Type 1 reactions are a reversal or upgrade of the cell-mediated immunity to *M leprae* antibodies, whereas type 2 reactions are the result of immune complexes attracting granulocytes and activation of complement and cytokine responses.[53] Both reactions may damage peripheral nerves with impairment of function and can occur at any time in the clinical course of the disease, independent of treatment. The World Health Organization thus recommends to follow up patients with leprosy for several years after an apparently successful treatment.[4,55,56]

This systematic review focused on the likelihood of disability among patients with leprosy reactions at the time of diagnosis. However, studies have reported a high risk of leprosy reactions after completion of multidrug therapy, requiring long-term follow-up with neurologic examinations.[4,10,57] The early identification of reactions and their prompt management with prednisone (1 to 2 mg/kg/d for ≥90 days) can prevent neuropathies and disability.[17]

The WHO Global Leprosy Strategy 2010-2020[7] aims to accelerate action toward a leprosy-free world, with a focus on the early detection of cases, before disabilities occur, and the prevention and early detection of disabilities among higher-risk groups by conducting active case-finding campaigns in highly endemic areas or communities. In this sense, our findings provide information to stakeholders regarding to the characterization of high-risk patients that should be prioritized and targeted to receive preventive interventions for the early detection and reduction of grade 2 disability in endemic areas.

Limitations

Our findings, however, should be interpreted with caution. All studies included were observational, patients were not randomized, and studies were often conducted with other primary objectives; therefore, the studies are susceptible to patient selection bias and the disability information may not have been collected systematically. Moreover, it was not possible to perform meta-analyses to explore whether age, schooling level, and socioeconomic status were associated with physical disability. Most studies, however, indicated that the prevalence of disability increases with age and that disability is inversely proportional to socioeconomic conditions and educational level. Education and income are considered determining factors for disease improvement and protective for the occurrence of disability.[2]

Conclusions

Despite these limitations, we demonstrate an association between the presence of physical disabilities and sex, MB leprosy, leprosy reactions, and a lepromatous presentation. These findings can guide the development of targeted interventions to identify individuals at early risk of physical disabilities and to inform education campaigns promoting early consultation to institute treatment for leprosy reactions and prevention of further physical disability. Long-term follow-up is necessary to monitor factors associated with development of disabilities, as are the provision of interventions promoting self-care, disability prevention, and the availability of rehabilitation services.

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