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REVIEW

Prevalence of beta thalassemia carriers in India: a systematic review and meta-analysis

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Abstract

A large number of studies have reported that the prevalence of beta thalassemia carriers in India varies by ethnic groups. The objective of this study was to conduct a systematic review of the published studies and conduct a meta-analysis to determine the prevalence of beta thalassaemia carriers in India. A PubMed database search using keywords "beta thalassaemia AND India" identified 1088 articles of which 69 articles were included in the review. Studies using diagnostic tests and methods recommended by the International Council for Standardization in Haematology were used for calculation of pooled prevalence. Pooled prevalence was calculated using a random effects model using Review Manager version 5.3. Studies had screened five categories of populations, that is, the general population; tribal groups, communities not belonging to tribal groups, persons with anemia, and persons referred with a suspicion of hemoglobinopathy. This heterogeneity contributed to a high pooled prevalence of beta thalassemia carriers of 8.23% (95% CI 7.36–9.10). Sub-group analysis however yielded 3.74% (95% CI 2.52–4.97) pooled prevalence of beta thalassemia carriers in the general population. It was 4.6% (95% CI 3.2–6.2) among tribal groups. Quality of prevalence studies was limited by methodological issues including non-random sampling methods, heterogeneity of population types screened, and lack of use of recommended diagnostic cut-offs. Prevalence of beta thalassemia carriers was similar in tribal populations and the general population, indicating the need to further investigate the prevalence of beta thalassemia carriers in tribal groups.

Keywords Prevalence · Beta thalassaemia · India · Review · Meta-analysis

Introduction

Beta thalassemias are genetic disorders with quantitative deficiency in the synthesis of the beta globin chains of hemoglobin. Patients with homozygous beta thalassaemia, referred to as beta thalassaemia major, are chronically anemic, are transfusion-dependent, and have a low life expectancy when optimal care is unavailable. Persons heterozygous for beta thalassaemia, referred to as carriers, are asymptomatic and mildly anemic (Galanello and Origa 2010). Magnitude of beta thalassaemia is obtained by measuring the prevalence of beta thalassaemia carriers (Hickman et al. 1999).

Estimates indicate that the global carrier prevalence ranges between 0.5 and 20% (Weatherall et al. 2006). Beta thalassemias are considered to be widespread particularly in the Indian sub-continent by virtue of its large population (Weatherall and Clegg 2001; Modell and Darlison 2008). There is no national estimate on the prevalence of beta thalassaemia carriers, although there are several studies in smaller geographical locations and defined populations to determine the prevalence of beta thalassaemia carriers.

These studies have examined diverse populations. Some studies have included persons from villages or towns, have been conducted at antenatal clinics, have included pregnant women, and have recruited students from academic institutions. There are several studies that have measured the prevalence of beta thalassemia carriers among tribal groups and among specific communities. Yet other studies have tested for beta thalassaemia carrier status among persons with anemia, patients suspected with hemoglobinopathies, or extended family members of patients with beta thalassaemia major (Jain et al. 1981; Jain et al. 1983; Choubisa 1985;

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Rao and Gorakshakar 1990; Choubisa 1991; Manglani et al. 1997; Balgir et al. 1999; Ambekar et al. 2001; Gajra et al. 2002; Ghosh et al. 2002; Choubisa et al. 2004; Chhotray et al. 2004; Balgir 2005a, b; Choubisa 2006; Sinha et al. 2006; Jawahirani et al. 2007; Colah et al. 2008; Mulchandani et al. 2008; Gupta et al. 2009; Kumar and Tamhankar 2009; Saraswathy 2009; Munshi et al. 2009; Choubisa 2009; Sachdev et al. 2010; Madan et al. 2010; Colah et al. 2010; Balgir 2010; Rao et al. 2010; Chandrashekar and Soni 2011; Dolai et al. 2012; Jain et al. 2012; Parthasarthy 2012; Patel et al. 2012; Bhukhanvala et al. 2012; Achoubi et al. 2012; Kulkarni et al. 2013; Philip et al. 2013; Rakholia and Chaturvedi 2013; Mohanty et al. 2013; Tiwari et al. 2013; Bhukhanvala et al. 2013; Baxi et al. 2013; Piplani et al. 2013; Baruah et al. 2014; Patel et al. 2014; Purohit et al. 2014; Sahoo et al. 2014; Verma et al. 2014; Chatterjee et al. 2015; Choudhuri et al. 2015; Mukhopadhyay et al. 2015; Nagar et al. 2015; Mohanty et al. 2015; Mondal and Mandal 2016; Teli et al. 2016).

The reported prevalence of beta thalassaemia carriers ranged from 0.2 to 21.8% (Munshi et al. 2009; Achoubi et al. 2012). Multicentric studies reported carrier prevalence estimates of 2.8 to 4.04% (Madan et al. 2010; Mohanty et al. 2013). Colah et al. 2010 has reported thalassaemia carrier frequencies by district, for the states of Gujarat and Maharashtra, and reported carrier frequencies ranging from 0.7 to 9.5% (Colah et al. 2010). The differences in the reported prevalence estimates between studies could be inherent population characteristics or methodological issues, such as use of different screening and diagnostic tests and by the use of different diagnostic cut-offs for HbA_2 levels (ranging from 3.0 to 4.5%). The purpose of this study was to systematically review these studies and conduct a meta-analysis to predict the number of beta thalassemia carriers in India.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guideline (Page et al. 2021).

Electronic literature search

The PubMed database (MEDLINE) was searched using the search terms ("beta thalassaemia"[All Fields] OR "beta-thalassemia"[MeSH Terms] OR "beta-thalassemia" [All Fields] OR ("beta"[All Fields] AND "thalassemia"[All Fields]) OR "beta thalassemia"[All Fields]) AND ("India"[MeSH Terms] OR "India"[All Fields]) in November 2022 which elicited 1088 articles. There were no restrictions on date of publication. The citations of eligible articles were screened to identify articles for potential inclusion in the review.

Study selection

All articles were screened for the possibility of extracting data on the number of beta thalassaemia carriers. Studies reporting the methodology in sufficient detail to extract relevant data were included. Studies were included in the review if they fulfilled the following criteria: (1) reported data on number of beta thalassaemia carriers and (2) were conducted in India. Studies were excluded if they were published before 1978 (as the first guideline for HbA_2 cut-off for carrier diagnosis had been issued in this year by the International Council for the Standardization of Haematology (ICSH) (Stephens et al. 2012). Mutation analysis studies, studies evaluating the sensitivity and specificity of diagnostic tests, studies screening persons post-blood transfusion, micromapping studies, and studies presenting duplicated data were excluded. Finally, 69 studies were selected for the review (Fig. 1). SD identified articles for extraction which was independently verified by AK. Any disputes were resolved through discussion.

Data extraction

A data extraction format was designed in MS Excel to extract data on the following study variables: study setting, geographical location of study, type of population characterized, description of population characterized, sampling method, sample size, study design, screening and diagnostic techniques used, diagnostic cut-offs used, informed consent administered, and ethics committee approval. The primary outcome was the number of beta thalassaemia carriers. The prevalence estimates of each study included in the review were verified by recalculating the prevalence from the numerator (number of beta thalassaemia carriers) and the denominator (total number of individuals screened). Quality of data was assessed by comparison of study designs, sampling methods, and whether screening and diagnostic methods used the case definitions as prescribed.

Screening for hemoglobinopathies primarily involves a hemogram used to detect microcytosis or a NESTROFT (Naked Eye Single Tube Red cell Osmotic Fragility Test) which is usually used in resource-limited or field-based settings (Traeger-Synodinos et al. 2014; Ministry of Health and Family Welfare. Government of India 2016). Diagnosis for hemoglobinopathies is done for samples with microcytosis by quantification of HbA_2 by electrophoresis, chromatography, HPLC, capillary and Hb electrophoresis, or/and DNA analysis using PCR-based methods, sequencing, reverse dot blot analysis, and microarrays (Traeger-Synodinos et al. 2014). The ICSH and the European Molecular

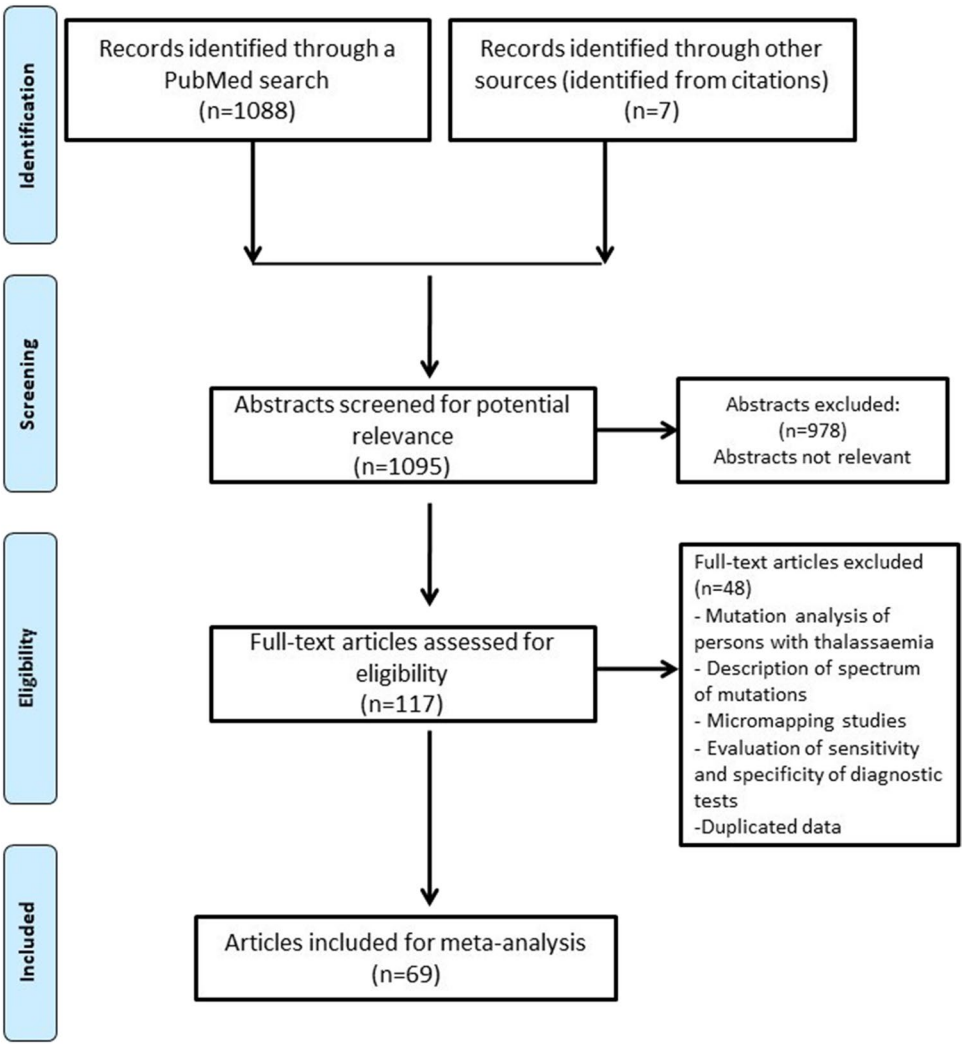

Fig. 1 Selection of studies for review (PRISMA)

Genetics Quality Network (EMQN) state that persons with $HbA_2 > 3.5\%$ should be diagnosed as carriers, and those in the range between 3.5 and 4.0% should be screened further using DNA analysis for silent beta thalassemia mutations, severe iron deficiency, or other hemoglobin variants (International Committee for Standardization in Haematology 1978; Stephens et al. 2012; Traeger-Synodinos et al. 2014).

Data analysis

Prevalence was calculated as the number of beta thalassaemia carriers per 100 individuals screened. Pooled prevalence was calculated in Review Manager (version 5.3) using the inverse variance method reported by Allagh et al. (2015 and Bhide and Kar (2018). A random effects model was used for meta-analysis due to the high heterogeneity between the studies ($I_2 > 95\%$, $p < 0.05$) and depicted using a forest plot. Prior to meta-analysis, standard error (SE) for each prevalence estimate was calculated using the formula $SE = \sqrt{p(1\text{-}p)/n}$ where p = proportion of individuals diagnosed with beta thalassaemia trait and n = total sample size for the study.

Results

Search resultss

The search strategy identified 1088 articles which were published between 1978 and 2022. Abstracts of these articles were screened, and a total of 69 articles were identified to be eligible for inclusion in the review (Fig. 1).

Study characteristics

The sample size of studies ranged from 100 to 287,258 individuals. Studies were reported from across the country, with 32% (22/69) from the eastern region (Balgir et al. 1999; Gajra et al. 2002; Chhotray et al. 2004; Balgir

2005a, b, 2010; Dolai et al. 2012; Jain et al. 2012; Mondal et al. 2012; Baruah et al. 2014; Purohit et al. 2014; Sahoo et al. 2014; Chatterjee et al. 2015; Choudhuri et al. 2015; Mukhopadhyay et al. 2015; Nagar et al. 2015; Mondal and Mandal 2016; Teli et al. 2016), 25% (17/69) from western India (Rao and Gorakshakar 1990; Manglani et al. 1997; Ambekar et al. 2001; Ghosh et al. 2002; Jawahirani et al. 2007; Colah et al. 2008; Mulchandani et al. 2008; Colah et al. 2010; Patel et al. 2012; Bhukhanvala et al. 2012; Philip et al. 2013; Rakholia and Chaturvedi 2013; Tiwari et al. 2013; Bhukhanvala et al. 2013; Purohit et al. 2014; Mohanty et al. 2015), 16% (11/69) from central (Jain et al. 1981; Jain et al. 1983; Choubisa 1985; Choubisa 1991; Choubisa et al. 2004; Choubisa 2006; Gupta et al. 2009; Tamhankar et al. 2009; Baxi et al. 2013), 13% (9/69) studies from the north (Sinha et al. 2006; Saraswathy 2009; Sachdev et al. 2010; Rao et al. 2010; Verma et al. 2014), 7% (5/69) from south India (Munshi et al. 2009; Chandrashekar and Soni 2011; Kulkarni et al. 2013), and 3% (2/69) studies from the northeast (De et al. 2006; Achoubi et al. 2012). There were 3/69 (4%) multicentric studies (Madan et al. 2010; Mohanty et al. 2013), and one study had not mentioned the location (Parthasarthy 2012) (Table 1).

Population sub-groups

The included studies surveyed populations with different levels of risk of being carriers of beta thalassemia, that is, general population, endogamous populations with tribal ethnicity, non-tribal populations practicing endogamy, patients with anemia, and persons clinically referred on suspicion of being a carrier of a hemoglobinopathy. Due to this variation, pooled prevalence estimates were made based on these categories.

Description of screening and diagnostic tests used

The screening tests used in the studies were clinical suspicion, NESTROFT, peripheral smear, and hemogram. The diagnostic tests used by the studies were electrophoresis (agar or cellulose acetate), high-performance liquid chromatography (HPLC), and molecular analysis (ARMS PCR, sequencing).

There were 65/69 (93%) studies that had used a screening procedure prior to diagnosis, of which 42/65 (63%) studies had used hemogram (Balgir et al. 1999; Ghosh et al. 2002; Balgir 2005a, b, 2010; De et al. 2006; Gupta et al. 2009; Tamhankar et al. 2009; Sachdev et al. 2010; Madan et al. 2010; Colah et al. 2010; Rao et al. 2010; Chandrashekar and Soni 2011; Dolai et al. 2012; Jain et al. 2012; Mondal et al. 2012; Parthasarthy 2012; Patel et al. 2012; Bhukhanvala et al. 2012, 2013; Philip et al. 2013; Mohanty et al. 2013; Tiwari et al. 2013; Baxi et al. 2013; Baruah et al. 2014; Chatterjee et al. 2015; Choudhuri et al. 2015; Mukhopadhyay et al. 2015; Nagar et al. 2015; Mondal and Mandal 2016; Teli et al. 2016), 9/65 (14%) studies had used NESTROFT (Jain et al. 1981; Ambekar et al. 2001; Jawahirani et al. 2007; Colah et al. 2008; Saraswathy 2009; Munshi et al. 2009; Achoubi et al. 2012; Kulkarni et al. 2013; Rakholia and Chaturvedi 2013), and 2/65 (4%) studies had examined a peripheral smear (Jain et al. 1983; Choubisa 1985) to screen for beta thalassaemia carriers. There were 13/65 (19%) studies that had used a combination of methods of NESTROFT, hemogram, and peripheral smear examination (Manglani et al. 1997; Gajra et al. 2002; Choubisa et al. 2004; Chhotray et al. 2004; Choubisa 2006; Sinha et al. 2006; Mulchandani et al. 2008; Choubisa 2009; Verma et al. 2014; Mohanty et al. 2015) for screening (Table 1). Of the 69 studies, 68 (97%) studies had reported the type of diagnostic test used. Of these, 23/68 (34%) studies had done HbA_2 analysis by electrophoresis (Jain et al. 1981; Jain et al. 1983; Choubisa 1985; Rao and Gorakshakar 1990; Choubisa 1991; Manglani et al. 1997; Balgir et al. 1999; Ghosh et al. 2002; Choubisa et al. 2004; Balgir 2005a, b; Choubisa 2006; Sinha et al. 2006; Jawahirani et al. 2007; Mulchandani et al. 2008; Choubisa 2009; Madan et al. 2010; Balgir 2010; Jain et al. 2012; Rakholia and Chaturvedi 2013; Tiwari et al. 2013), 30/68 (41%) studies had done HbA_2 analysis by HPLC (Gupta et al. 2009; Sachdev et al. 2010; Colah et al. 2010; Rao et al. 2010; Chandrashekar and Soni 2011; Dolai et al. 2012; Mondal et al. 2012; Parthasarthy 2012; Patel et al. 2012; Philip et al. 2013; Mohanty et al. 2013, 2015; Baruah et al. 2014; Verma et al. 2014; Chatterjee et al. 2015; Choudhuri et al. 2015; Mukhopadhyay et al. 2015; Mondal and Mandal 2016; Teli et al. 2016), and one study (Sahoo et al. 2014) had used ARMS PCR for carrier diagnosis. There were 12/68 (17%) studies that had used mutation analysis by ARMS PCR for carrier detection in combination with HPLC and electrophoresis methods (Gajra et al. 2002; Chhotray et al. 2004; De et al. 2006; Saraswathy 2009; Tamhankar et al. 2009; Munshi et al. 2009; Achoubi et al. 2012; Baxi et al. 2013; Purohit et al. 2014; Nagar et al. 2015), whereas 6/68 (9%) studies had used a combination of HPLC and cellulose electrophoresis methods for carrier detection (Ambekar et al. 2001; Colah et al. 2008; Patel et al. 2012; Bhukhanvala et al. 2012, 2013) (Table 1).

Prevalence of beta thalassaemia carriers

Group I: general population

There were 28/69 studies which had screened 703,615 persons, of which 33,951 were diagnosed as beta thalassaemia carriers (Table 1). The population included students from academic institutions ($n=4$, 14%) (Tamhankar et al. 2009; Madan et al. 2010), pregnant women from antenatal

Table 1 Data summarizing methodologies adopted by included studies and presented by study groups

Sr. no	Study	Region	Community/ hospital setting/sec-ondary data from hospital records	Population	Sampling procedure	Screening methods	Diagnostics	Sample size	Prevalence of carriers
Group I: general population									
1	Patel et al. 2021	West	Community	Healthy indi-viduals	Non-random	Hemogram	HPLC	4197	0.6%
2	Maji et al. 2020	East	Community	Healthy indi-viduals	Not stated	Hemogram	HPLC	287,258	7.23%
3	Chatterjee et al. 2015	East	Secondary data from hospital records	Healthy indi-viduals and pregnant women	Non-random	Hemogram	HPLC	18,166	9.01%
4	Nagar et al. 2015	East	Community	Healthy indi-viduals	Non-random	Hemogram	HPLC, ARMS PCR	1642	3.41%
5	Sahoo et al. 2014	East	Hospital	Healthy indi-viduals	Non-random	Not done	ARMS PCR, Sequencing	267	4.5%
6	Mohanty et al. 2013	All regions	Community and Hos-pital	Healthy indi-viduals and pregnant women	Non-random	Hemogram	HPLC	56,780	2.78%
7	Achoubi et al. 2012	East	Community	Healthy indi-viduals	Random	NESTROFT	HPLC, PCR	599	0.16%
8	Bhukhanvala et al. 2012	West	Community	Healthy indi-viduals	Non-random	Hemogram	Electrophore-sis, HPLC	34,364	3.20%
9	Dolai et al. 2012	East	Community	Healthy indi-viduals	Non-random	Hemogram	HPLC	35,413	10.38%
10	Jain et al. 2012	East	Review of records	Healthy indi-viduals	Non-random	Hemogram	Electropho-resis	1562	8.13%
11	Patel et al. 2012	West	Community	Healthy indi-viduals	Non-random	Hemogram, sickling test	Electrophore-sis, HPLC	32,857	4.37%
12	Madan et al. 2010	North, West	Community	Healthy indi-viduals	Random	Hemogram	Electrophore-sis, PCR	11,090	4.04%
13	Colah et al. 2010	West	Community and hospital	Healthy indi-viduals and pregnant women	Non-random	Hemogram	HPLC, reverse dot blot	17,262	3.06%
14	Tamhankar et al. 2009	North	Community	Healthy indi-viduals	Non-random	Hemogram	HPLC, ARMS PCR	939	2.87%
15	De et al. 2006	North East	Community	Healthy indi-viduals	Random	Hemogram	Electrophore-sis, ARMS PCR	1726	2.9%
16	Choubisa 2006	West	Community and hospital	Healthy indi-viduals	Random	Hemogram, NESTROFT	Electropho-resis	1415	3.81%
17	Choubisa 1991	West	Community	Healthy indi-viduals	Non-random	not stated	Electropho-resis	2922	3.28%
18	Gosavi et al. 2021	South	Hospital	Pregnant women	Non-random	NESTROFT, Hemogram	HPLC	441	3.6%
19	Choudhuri et al. 2015	East	Hospital	Pregnant women	Non-random	Hemogram	HPLC	20,883	4.1%
20	Patel et al. 2014	West	Hospital	Pregnant women	Non-random	Hemogram	HPLC	111,426	0.25%
21	Baxi et al. 2013	Central	Hospital	Pregnant women	Non-random	Hemogram	HPLC, ARMS PCR	1006	2.78%

Table 1 (continued)

Sr. no	Study	Region	Community/ hospital setting/sec-ondary data from hospital records	Population	Sampling procedure	Screening methods	Diagnostics	Sample size	Prevalence of carriers
22	Bhukanvala et al. 2013	West	Hospital	Pregnant women	Non-random	Hemogram	Electrophore-sis, HPLC	3009	3.38%
23	Kulkarni et al. 2013	South	Hospital	Pregnant women	Non-random	NESTROF	-	210	8.57%
24	Philip et al. 2013	West	Hospital	Pregnant women	Non-random	Hemogram	HPLC	2119	4.86%
25	Tiwari et al. 2013	West	Hospital	Pregnant women	Non-random	Hemogram	Electropho-resis	100	3.0%
26	Colah et al. 2008	West	Hospital	Pregnant women	Non-random	NESTROFT	Electrophore-sis, HPLC	61,935	1.6%
27	Sinha et al. 2006	North	Hospital	Pregnant women	Non-random	Hemogram, NESTROFT	Electropho-resis	120	5.83%
28	Gajra et al. 2002	East	Hospital	Pregnant women	Non-random	NESTROFT, Hemogram	Electrophore-sis, ARMS PCR	1962	7.03%
Group II: tribal communities									
1	Dixit et al. 2022	East	Community	Tribes	Random	Hemogram	HPLC, PCR	1461	0.34%
2	Chourasia et al. 2020	Central	Community	Tribes	Non-random	Hemogram	HPLC	56	1.4%
3	Mohanty et al. 2015	West, East South	Community	Tribes	Random	NESTROFT, Hemogram	HPLC	15,200	2.41%
4	Purohit et al. 2014	East	Community	Tribes	Not men-tioned	Not mentioned	HPLC, PCR	594	3.4%
5	Balgir 2010	East	Community	Tribes	Random	Hemogram	Electropho-resis	767	6.25%
6	Choubisa 2009	West	Community	Tribes	Non-random	NESTROFT, Hemogram	Electropho-resis	368	7.6%
7	Balgir et al. 2005a	East	Community	Tribes	Random	Hemogram	Electropho-resis	836	6.45%
8	Choubisa et al. 2004	West	Community and Hos-pital	Tribes	Random	NESTROFT, Hemogram	Electropho-resis	3163	5.75%
9	Ghosh et al. 2002	West	Community	Tribes	Non-random	Hemogram	Electropho-resis	481	1.87%
10	Balgir et al. 1999	East	Community	Tribes	Random	Hemogram	Electropho-resis	465	3.0%
11	Rao and Goraksha-kar 1990	West	Community	Tribes	Not men-tioned	Not done	Electropho-resis	1037	2.98%
12	Jain et al. 1983	West	Community	Tribes	Not men-tioned	Hemogram	Electropho-resis	912	5.34%
13	Jain et al.1981	West	Community	Tribes	Not men-tioned	NESTROFT	Electropho-resis	280	2.5%
Group III: ethnic communities									
1	Nigam et al. 2020	North	Community	Healthy indi-viduals	Not men-tioned	None	HPLC	493	12.98%
2	Rakholia and Chaturvedi 2013	West	Community	Healthy indi-viduals	Random	NESTROFT	Electropho-resis	550	17.6%

Table 1 (continued)

Sr. no	Study	Region	Community/hospital setting/secondary data from hospital records	Population	Sampling procedure	Screening methods	Diagnostics	Sample size	Prevalence of carriers
3	Bhukhanvala et al. 2012	West	Community	Communities	Not mentioned	Hemogram	Electrophoresis, HPLC	9447	3.9%
4	Saraswathy 2009	North	Community	Endogamous community	Not mentioned	NESTROFT	Electrophoresis, ARMS PCR	210	8.6%
5	Mulchandani et al. 2008	West	Community	Endogamous community	Not mentioned	NESTROFT, Hemogram	Electrophoresis	446	16.81%
6	Jawahirani et al. 2007	West	Community	Endogamous community	Not mentioned	NESTROFT	Electrophoresis	1563	16.3%
7	Choubisa et al. 2004	West	Community and Hospital	Endogamous communities	Random	NESTROFT, Hemogram	Electrophoresis	1189	3.03%
8	Manglani et al. 1997	West	Community	Endogamous community	Non-random	NESTROFT, Hemogram	Electrophoresis	2525	12.19%
9	Choubisa 1985	West	Community and Hospital	Endogamous community	Non-random	Hemogram	Electrophoresis	706	1.84%
Group IV: persons with anemia									
1	Sabitha Rani et al. 2022	South	Hospital	Children in pediatrics ward	Non-random	Hemogram	Electrophoresis	2928	1.16%
2	Bhargava et al. 2020	North	Hospital	Anemia cases	Non-random	Hemogram	HPLC	1353	7.24%
3	Ray and Jena 2019	East	Hospital	Anemia cases	Non-random	Hemogram	HPLC	21,371	11.78%
4	Tripathi et al. 2018	North	Hospital	Anemia cases	Non-random	NESTROFT, Hemogram	HPLC	17,047	6.95%
5	Teli et al. 2016	East	Hospital	Anemia cases	Non-random	Hemogram	HPLC	1200	5.83%
6	Verma et al. 2014	North	Hospital	Anemia cases	Non-random	Hemogram, peripheral blood smear	HPLC	1317	13.9%
7	Baruah et al. 2014	East	Hospital	Anemia cases	Review of records	Hemogram	HPLC	9000	3.48%
8	Parthasarthy 2012	-	Hospital	Anemia cases	Non-random	Hemogram	HPLC	200	19.5%
9	Gupta et al. 2009	Central	Hospital	Anemia cases	Non-random	Hemogram	HPLC	955	9.5%
10	Munshi et al. 2009	South	Hospital	Anemia cases	Non-random	NESTROFT	HPLC, ARMS PCR, reverse dot blot	1592	21.79%
11	Tamhankar et al. 2009	North	Hospital	Anemia cases	Non-random	Hemogram	HPLC, PCR	1348	16.02%
12	Balgir 2005b	East	Hospital	Anemia cases	Non-random	Hemogram	Electrophoresis	1015	18.2%
13	Chhotray et al. 2004	East	Hospital	Anemia cases	Non-random	Hemogram, NESTROFT	Electrophoresis, PCR	520	19.8%

Table 1 (continued)

Sr. no	Study	Region	Community/hospital setting/secondary data from hospital records	Population	Sampling procedure	Screening methods	Diagnostics	Sample size	Prevalence of carriers
Group V: persons with suspicion of hemoglobinopathy									
1	Sonkawade et al. 2022	West	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram, NESTROFT	HPLC	117	35%
2	Mondal and Mandal 2016	East	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	119,336	4.6%
3	Bhattacharya et al. 2014	East	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC, ARMS PCR	660	26%
4	Philip et al. 2013	West	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	2216	15.80%
5	Jain et al. 2012	East	Review of hospital records	Suspicion of hemoglobinopathy	Non-random	Hemogram	Electrophoresis	2261	22.06%
6	Mondal et al. 2012	East	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	958	17.64%
7	Chandrashekar and Soni 2011	South	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	543	37.9%
8	Rao et al. 2010	North	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	800	18.12%
9	Sachdev et al. 2010	North	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC	2600	8.92%
10	Tamhankar et al. 2009	North	Hospital	Suspicion of hemoglobinopathy	Non-random	Hemogram	HPLC, PCR	394	58.62%
11	Ambekar et al. 2001	West	Hospital	Suspicion of hemoglobinopathy	Non-random	NESTROFT	Electrophoresis, HPLC	1291	7.05%

clinics ($n=11$, 39%) (Gajra et al. 2002; Sinha et al. 2006; Colah et al. 2008; Kulkarni et al. 2013; Philip et al. 2013; Tiwari et al. 2013; Bhukhanvala et al. 2013; Baxi et al. 2013; Patel et al. 2014; Choudhuri et al. 2015), and individuals selected from community settings ($n=4$, 14%) (Choubisa 1991, 2006; Bhukhanvala et al. 2012; Achoubi et al. 2012), and 9/29 (31%) studies had sampled the population to be screened from multiple sources, i.e., community, healthcare, and academic institutions (Choubisa 1991, 2006; Colah et al. 2010; Dolai et al. 2012; Jain et al. 2012; Patel et al. 2012; Mohanty et al. 2013; Sahoo et al. 2014; Chatterjee et al. 2015; Nagar et al. 2015) Studies screening the general population had larger sample sizes as compared to studies screening other population types. Of these, 15/28 (54%) studies were eligible (Choubisa 1991, 2006; Gajra et al. 2002; Tamhankar et al. 2009; Madan et al. 2010; Jain et al. 2012; Patel et al. 2012; Bhukhanvala et al. 2012, 2013; Achoubi et al. 2012; Baxi et al. 2013; Sahoo et al. 2014; Nagar et al. 2015). They included 197,735 persons of which 3721 were beta thalassaemia carriers. Pooled prevalence of beta thalassaemia carriers in the general population was calculated to be 3.74% (95% CI 2.52–4.97) (Fig. 2a).

Group II: tribal communities

There were 14 studies that had screened a total of 24,287 individuals from 41 communities, and 973 persons were diagnosed as beta thalassaemia carriers (Table 1). The pooled prevalence of beta thalassaemia carriers was calculated from 8/14 (57%) eligible studies which had screened

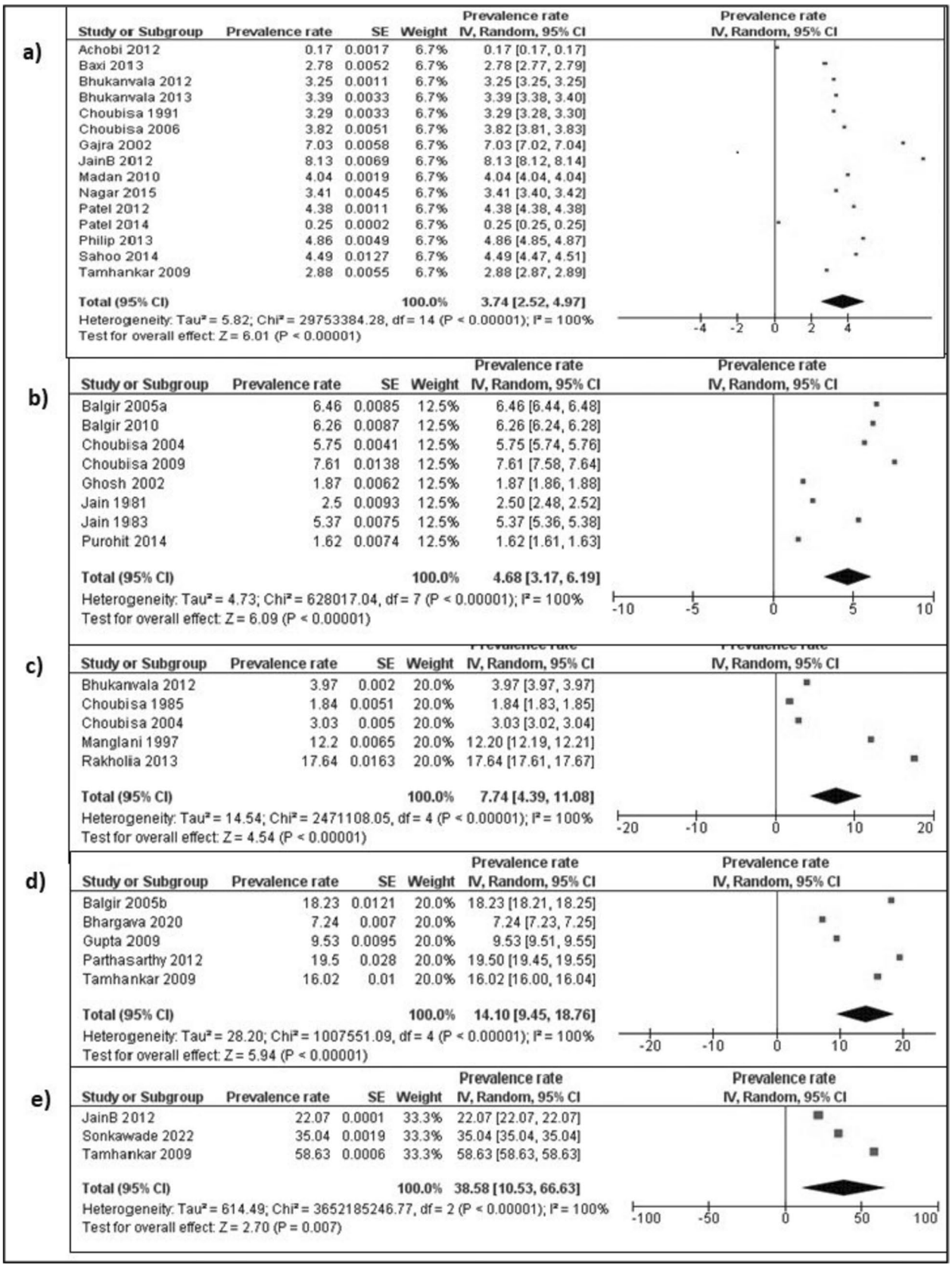

Fig. 2 Pooled prevalence of beta thalassaemia carriers in **a** general population, **b** tribal communities, **c** communities, **d** persons with anemia, **e** persons with suspicion of hemoglobinopathy

4650 persons of which 263 were beta thalassaemia carriers (Jain et al. 1981; Jain et al. 1983; Choubisa et al. 2004; Balgir 2005a; Choubisa 2009; Balgir 2010; Purohit et al. 2014) Pooled prevalence of beta thalassaemia carriers in the tribal communities was estimated to be 4.68% (95% CI 3.17–6.19) (Fig. 2b).

Group III: communities not belonging to tribal groups

Members of ethnic communities were targeted for screening either because there was a purported higher prevalence of beta thalassaemia amongst the members or they practiced endogamy, i.e., marriage within the community. There were a total of 9 eligible studies that screened 16,943 individuals from five communities (Table 1). There were 4/9 (36%) studies that had screened only Sindhis ($n=2769$ individuals) (Manglani et al. 1997; Jawahirani et al. 2007; Mulchandani et al. 2008; Saraswathy 2009; Rakholia and Chaturvedi 2013) because beta thalassemias are considered to be prevalent in this community. The other communities screened were different castes and sub-castes of Gujaratis ($n=5003$), Muslims ($n=4870$), scheduled castes ($n=1895$), Punjabis ($n=622$), Tharu ($n=493$), and Maharashtrians ($n=109$). The pooled prevalence was calculated from 5/9 (56%) eligible studies which had screened 14,231 persons of which 799 were carriers. The pooled prevalence of beta thalassemia carriers in communities not belonging to tribal groups is 7.74% (95% CI 4.39–11.08) (Fig. 2c). This pooled estimate has to be considered with caution since pooling data from these different communities themselves increases heterogeneity.

Group IV: persons with anemia

Studies in this group had screened patients with anemia. There were 13 studies that had screened 59,846 patients with anemia, of which 5630 were beta thalassaemia carriers (Chhotray et al. 2004; Balgir 2005b; Gupta et al. 2009; Tamhankar et al. 2009; Munshi et al. 2009; Parthasarthy 2012; Piplani et al. 2013; Baruah et al. 2014; Verma et al. 2014; Teli et al. 2016) (Table 1). The pooled prevalence of beta thalassaemia carriers was calculated from 5/13 (39%) eligible studies which had screened 3917 persons of which 644 were beta thalassaemia carriers. The pooled prevalence of beta thalassaemia carriers in persons with anemia was calculated to be 14.1% (95% CI 9.45–18.76) (Fig. 2d).

Group V: persons with suspicion of hemoglobinopathy

This group included studies that had screened individuals with a high index of suspicion such as extended family members or patients suspected with hemolytic anemia. There were 11 studies that had screened 131,176 individuals with a suspicion of hemoglobinopathy, of which 7630 were beta thalassaemia carriers (Ambekar et al. 2001; Sachdev et al. 2010; Rao et al. 2010; Chandrashekar and Soni 2011; Jain et al. 2012; Mondal et al. 2012; Philip et al. 2013; Verma et al. 2014; Mukhopadhyay et al. 2015; Mondal and Mandal 2016). The pooled prevalence of beta thalassaemia carriers was calculated from 3/12 (25%) eligible studies, which had screened 2772 persons of which 771 were beta thalassaemia carriers (Chhotray et al. 2004; Balgir 2005b; Tamhankar et al. 2009; Munshi et al. 2009; Parthasarthy 2012). Thus, the pooled prevalence of beta thalassaemia carriers in persons with suspicion of hemoglobinopathy was estimated to be 38.58% (95% CI 10.53–66.63) (Fig. 2e).

It is noteworthy that when all studies are included including 38/69 (55%) studies not using the recommended diagnostic cut-offs, the pooled prevalence of beta thalassaemia carriers was 8.23% (95% CI 7.36–9.10). Figure 3 shows that while few regions of the country had multiple studies reporting data for different population sub-groups, there was no reliable data for other parts of the country.

Discussion

The systematic review identified that there were more than a thousand published studies on beta thalassemia in India. However, only a limited number were prevalence studies reporting the magnitude of beta thalassemia carriers. The meta-analyses identified methodological issues that could influence prevalence estimates. The first methodological issue was that studies had been conducted in diverse populations, with different levels of risk. For example, studies conducted among school children would represent the true prevalence in the general population, while prevalence studies from tribal communities would have a higher prevalence due to endogamy and known high prevalence of the circulating allele. Similarly, patients with chronic anemia referred for beta thalassaemia testing would represent a biased sample and therefore may represent higher prevalence.

The second source of possible error was the lack of random sampling or lack of description of the method by which the sample had been drawn. Only 17% of studies had used random sampling methods, and 85% of studies either had not mentioned the type of sampling method used or had provided insufficient information to decipher the method used. The third methodological issue that could influence pooled prevalence estimates was the use of different screening tests and different diagnostic cut-offs used for HbA_2 analysis, in lieu of those recommended by ICSH and EMQN. Such sources of error were evident in the meta-analysis, as only half of the studies in each sub-group were eligible for analysis.

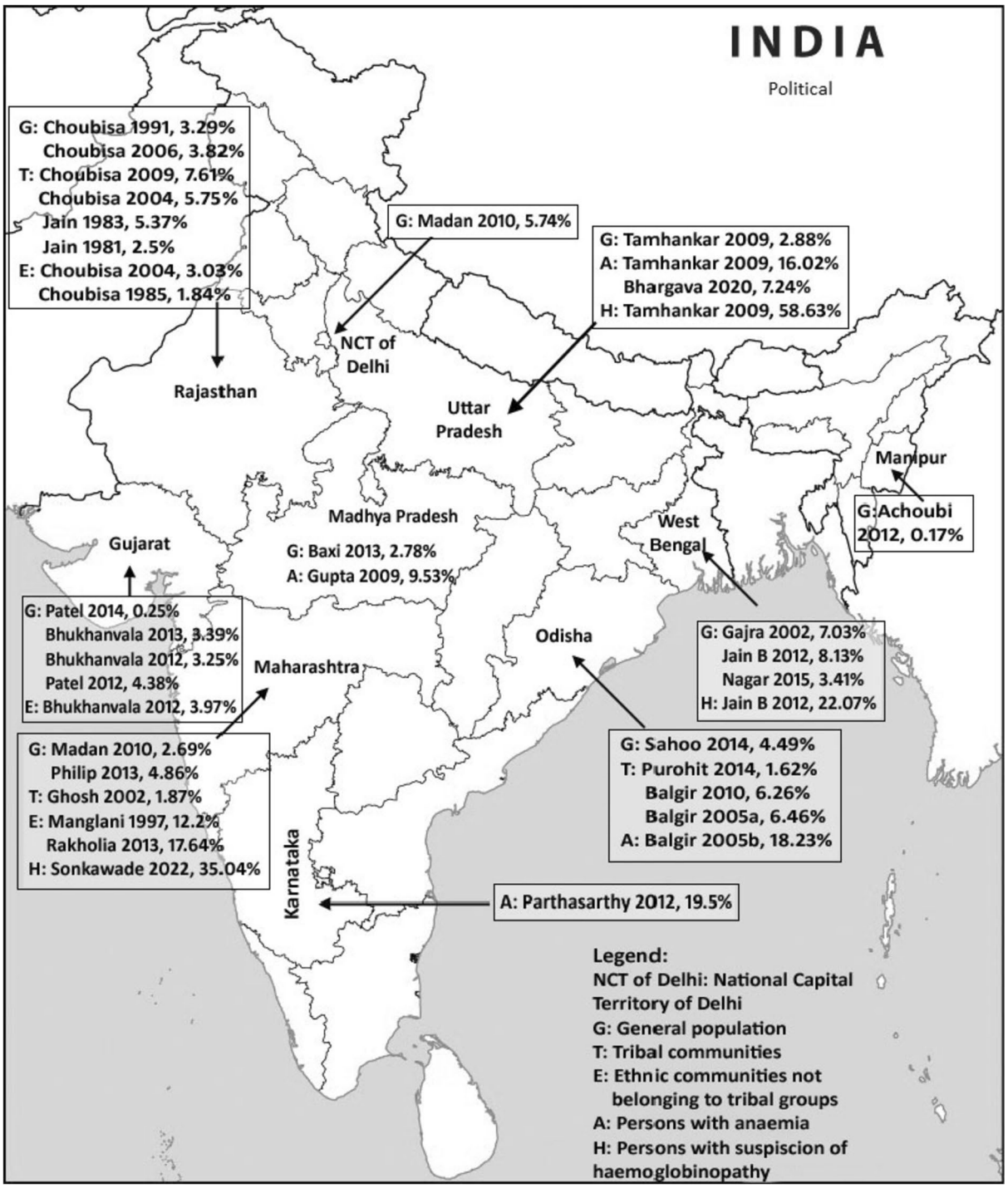

Fig. 3 Reported prevalence of beta thalassaemia carriers in India in the general population (G); tribal communities (T); ethnic communities not belonging to tribal groups I; persons with anemia (A); persons with suspicion of a hemoglobinopathy (H)

The meta-analysis circumvented these sources of error by conducting sub-group analyses and by including only those studies that reported using the recommended diagnostic cut-offs. Without this, the pooled prevalence estimate was inordinately high at over 8%. The results of the meta-analysis confirm the high prevalence of beta-thalassemia carriers in the general population (3.7%). These estimates have significant public health implications. Using a 4% carrier prevalence and the method of Hickman et al. 1999, an estimated 8740 children with beta thalassaemia major may be born each year in India, in the absence of preventive interventions. An equivalent prevalence of 4% in tribal communities is indicative of

the need to further investigate beta thalassaemia prevalence in these populations. It is important to point out that eligible studies, measuring the prevalence of beta thalassemia in tribal populations, were limited. It is noteworthy that a program for the elimination of sickle cell disease has been launched recently in India (Ministry of Health and Family Welfare. Government of India 2023). The results of this analysis indicate that beta thalassemia may be as widespread as sickle cell disease, and it may be relevant to increase the scope of this project to include all hemoglobinopathies common in India.

Strengths and limitations of the study

The limitation of this study is that only a single database was used to search for studies. However, references of all articles were scanned in order to identify possible studies published in local journals and articles not indexed in the PubMed database.

Conclusions

Despite a large body of literature on beta thalassemia prevalence in India, this study identified several methodological issues that could influence prevalence estimates. These include unclear methodologies, non-random samples, small size of studies, screening of heterogeneous population groups, and not using internationally recommended diagnostic cut-offs. Data from 69 studies identified approximately 4% prevalence of beta thalassemia carriers in the general population. A similar high prevalence of beta thalassemia among tribal population groups indicates the need for including screening, prevention, and care for beta thalassemia in the ongoing project for elimination of sickle cell disease in India. In light of the high prevalence of beta thalassemia carriers in India, methodologically rigorous studies are needed to assist public health decision-making for prevention and care.

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Author contribution SD designed the study, conducted the literature review, analysed the data and drafted the manuscript. AK conceptualized the study, supervised the search, selection of data and data analyses, wrote the final draft of the manuscript.

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Data Availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval Secondary data analysis, and therefore did not require review of the Institutional Ethics Committee.

Consent to participate Not applicable.

Conflict of interest Sumedha Dharmarajan and Anita Kar declare that they have no conflict of interest.

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