EC

ORIGINAL ARTICLE EPID

The association between parental consanguinity and primary immunodeficiency diseases: A systematic review and meta-analysis

Hasti Hadizadeh[1,2], Masoud Salehi[1,2], Shabnam Khoramnejad[1], Kia Vosoughi[1,2] & Nima Rezaei[2,3]

[1]Student Research Committee, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran; [2]Systematic Review and Meta-Analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran; [3]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

To cite this article: Hadizadeh H, Salehi M, Khoramnejad S, Vosoughi K, Rezaei N. The association between parental consanguinity and primary immunodeficiency diseases: A systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017: **28**: 280–287.

Keywords
consanguinity; epidemiology; meta-analysis; prevalence; primary immunodeficiencies

Correspondence
Masoud Salehi, Student Research Committee, Faculty of Medicine, Iran University of Medical Sciences, Hemmat Expressway, Tehran, Iran
Tel and Fax: +982186703072
E-mail: mmasood.salehi@gmail.com

Accepted for publication 25 November 2016

DOI:10.1111/pai.12685

Abstract

Background: We aimed to establish the prevalence of parental consanguinity among patients with primary immunodeficiency diseases (PID) and compare the prevalence with the general population.
Method: We searched PubMed, EMBASE, and Scopus for studies mentioning parental consanguinity prevalence in patients with PID and calculated the prevalence odds ratio (POR) of parental consanguinity in each study, compared to a matched healthy population.
Results: We identified 21 eligible studies with a total population of 18091 accounting for sample overlap. The POR among studies on a sample of mixed patients with PID ranged from 0.6 to 21.9 with the pooled POR of 3.0 ($p < 0.001$; $I^2 = 89\%$, 95% CI: 2.5–3.7).
Conclusion: PIDs with an autosomal recessive pattern of inheritance had significant odds of parental consanguinity compared to the healthy population, a phenomenon not observed in other inheritance patterns. Determining the extent of the impact that consanguinity imposes upon the progeny paves the way for convincing healthcare policymakers in highly consanguineous communities to act more diligently in informing the masses about the consequences of practicing inbreeding.

Primary immunodeficiencies (PIDs) are a diverse group of rare, chronic disorders (1) that causes immune dysregulation and imbalance, leading to increased susceptibility to microorganisms and infections, the frequent occurrence of allergy, and predisposition to the development of immunologic disorders, autoimmune diseases, and malignancies (2).

Most primary immunodeficiency diseases are inherited. Advances in molecular biology have shown various primary biologic defects in most of these disorders. The mode of inheritance in most primary immunodeficiency diseases is in one of these ways: X-linked recessive, autosomal recessive (AR), or autosomal dominant (AD) (3).

Consanguineous marriage—defined as a union between two persons related as second cousins or closer—increases the risk of AR disorders (4, 5). As the probability that the offspring of consanguineous unions will inherit mutated AR gene increases, the risk for recessive disorders is probably higher in the offspring of consanguineous parents (6).

Knowing more about the impacts of consanguineous marriage helps to implement appropriate community programs to improve family health. To provide more evidence on the contribution of consanguineous marriage in primary immunodeficiency diseases (PID), this systematic review, and meta-analysis, aims to summarize (i) the worldwide prevalence of parental consanguinity among patients with PIDs and (ii) the prevalence odds ratio (POR) for parental consanguinity in patients with PID compared to general population.

Materials and methods

We conducted this systematic review and meta-analysis according to PRISMA statement guidelines (7).

Data sources and search strategies

We constructed an electronic search in PubMed, EMBASE, and Scopus databases to gather articles published up to May 2016. Our target population was patients diagnosed with any diseases categorized under the term 'Primary Immunologic Deficiency Syndrome'.

This study's primary outcome was the consanguinity prevalence among patients' parents. We combined the key words and MeSH terms for 'Primary Immunologic Deficiency Syndrome' and 'consanguinity' using the term 'AND'.

Study selection

Inclusion criteria were as follows: (i) English language studies, (ii) study designed as cross-sectional, prospective, or retrospective cohort, (iii) data collected from national registries, national referral centers for immunodeficiency diseases, national surveys addressing clinical immunologists throughout the countries, or multiple centers, (iv) consanguinity prevalence measured by any definition, (v) obtaining data on patients with PIDs, (vi) PID diagnosed by a specialist, (vii) PID diagnosed by any diagnostic criteria.

Exclusion criteria were as follows: (i) the presence of selection bias, (ii) overlap of the database or patients included in studies performed in a single country, (iii) not addressing patients with PID, separately.

A team of two medical doctors performed the screening process.

Data extraction and methodological quality

The data for each study were extracted using a data extraction sheet that included the following:

- Article's ID
- Original country of the study
- Study design
- Study's time span
- The population characteristics
- Parental consanguinity prevalence
- Possible biases

The extracted articles went under critical analysis using Munn et al. (8) Critical Appraisal tool for systematic reviews addressing questions of prevalence. The authors resolved disagreements by consensus. Eventually, studies were graded as 'High', 'Moderate', or 'Low' quality, and then, the low-quality articles were omitted.

Statistical analysis

We analyzed data using STATA 13.0 software (Stata-Crop. 2013. Stata Statistical Software: Release 13, College Station, TX). We used 'metan' command to generate pooled prevalence and RevMan 5.3 software (9) to generate forest plots.

The included studies were stratified first according to:

1 Geographic region based on world health organization (WHO) classification (10):
   - The Americas
   - Europe
   - the Eastern Mediterranean
   - the Western Pacific
2 The most common types of PIDs in the included articles:
   - Common variable immunodeficiency (CVID)
   - Selective IgA Deficiency (SIgAD)
   - severe combined immunodeficiency (SCID)
   - agammaglobulinemia
   - IgG subclass deficiency (IgGSD)
   - chronic granulomatous disease (CGD)
   - ataxia telangiectasia (AT)
   - DiGeorge syndrome (DGS)
   - Wiskott–Aldrich syndrome (WAS)
   - hyper-IgE syndrome (HIES)
   - leukocyte adhesion deficiency (LAD)
   - Chediak-Higashi syndrome (CHS)

Consanguinity prevalence in population

We obtained the information about the prevalence of consanguinity in the general population (the denominator) from national data that most closely matched the community of the study on patients with PID.

There were times when the study of patients with PID was performed in a large population/country like China where the practicing of consanguinity varies in different provinces. In such cases, we weighted consanguinity prevalence in the population based on the same composition as patients with PID.

Same as above, for one study consisting of data mainly from eight countries in Europe (11), we weighted the consanguinity prevalence in each country.

Exploring heterogeneity

We estimated the summary of odds ratios using the Mantel–Haenszel method. To assess heterogeneity between studies, we used I^2 statistics (12) as well as the p-value from Cochran's Q (13). In cases of low heterogeneity, we performed the meta-analysis using fixed effect model (14). When there was moderate, substantial, or considerable heterogeneity (15), we used random-effects model.

Results

Fig. 1 summarizes the literature search process. Fig. 2 depicts the statistics of the 21 studies that passed the quality appraisal. The final 21 studies were published from December 1985 to January 2016; data were collected since 1963 up until 2014. The sum of studies' sample sizes reached 24968; but, as there were times that we included more than one study from a country, we omitted the potential duplicate patients, so the number of individuals reached a total of 18091 patients diagnosed with different types of PIDs. Eleven studies' data were extracted from national registries, six were carried out on patients from referral centers for immunodeficiency diseases, three were conducted using national surveys addressing clinical

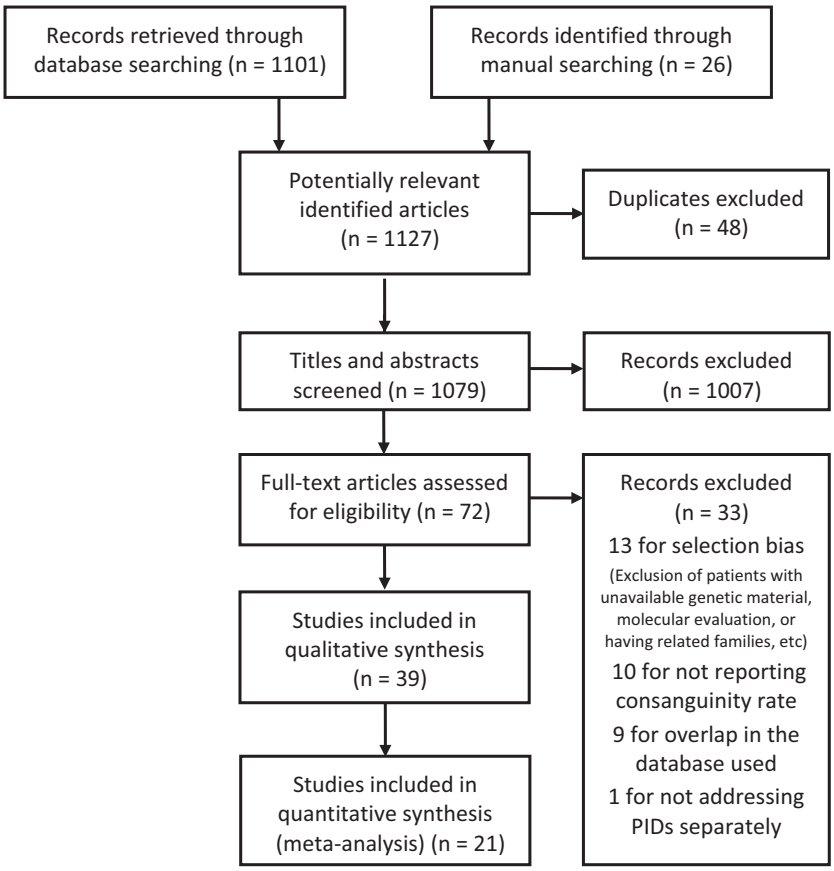


Figure 1 Flow diagram of the review process.

immunologists throughout the countries, and one was carried out based on data from multiple centers.

The most common diagnostic criteria were based on The European Society for Immunodeficiencies (ESID) and The International Union of Immunological Societies (IUIS) (11, 16–27).

Among all, only three studies were conducted on a particular type of PID (28–30). Overall male-to-female ratio was 1.44:1. Based on twelve studies, the mean age at diagnosis ranged from 12.0 to 74.5 months with considerable heterogeneity throughout the studies ($p < 0.001$; $I^2 = 96.5\%$). The random-effects pooled mean age of patients at the time of diagnosis was 43.6 months (95% CI: 36.9–50.4).

Table 1 shows the studies with their characteristics in details. The study with the lowest prevalence of parental consanguinity was from China with 2% (31), and the highest rated consanguinity was from a study from Oman, which was 81% (22).

To speculate the overall consanguinity prevalence in patients with PID of each geographic region, we meta-analyzed the consanguinity prevalence from articles that included all patients with PID regardless of their subtype (we omitted three studies (28–30) that were on a particular PID subtype and four studies (18, 23, 26, 27) that were from the same database as a larger study (11) to exclude the potential duplicates). Considering the high heterogeneity, the pooled consanguinity prevalence from the random-effect analysis was 65.7% ($p < 0.001$; $I^2 = 87.6$, 95% CI: 57.8–73.6) in patients with PID of Eastern Mediterranean region, 5.6% ($p < 0.001$; $I^2 = 98.3$, 95% CI: −0.8–12%) in Europe, and 2.3% (p: 0.712; $I^2 = 0\%$, 95% CI: 0.9–3.7%) in the Western Pacific.

Our findings revealed that Eastern Mediterranean communities tended to engage in consanguineous relationships widespread. Particularly, people of Middle Eastern countries were on top of the list, with Oman and Saudi Arabia being the first (56.3% and 56.0%, respectively).

Overall, the range of odds ratios stretched from 0.6 (Turkey)—with a sample of mixed subtypes of PIDs, through 117 (Australia)—which shows the ratio in patients with SCID. Among the studies with a sample of mixed subtypes of patients with PID, the French study sat at highest with an odds ratio of 21.9.

Fig. 3 illustrates the output of the meta-analysis of overall POR estimation. The pooled odds ratio (random-effects) was 3.02 ($p < 0.001$; $I^2 = 89.1\%$, 95% CI: 2.46–3.70).

By going through the articles and looking for the prevalent subtypes in each study, the analysis team agreed on 12 most common diseases to be included in further investigations. These specified diseases constitute 50% of all of our study patients. Fig. S1 portrays the distribution of these subtypes and indicates their proportion in relevance to the whole.

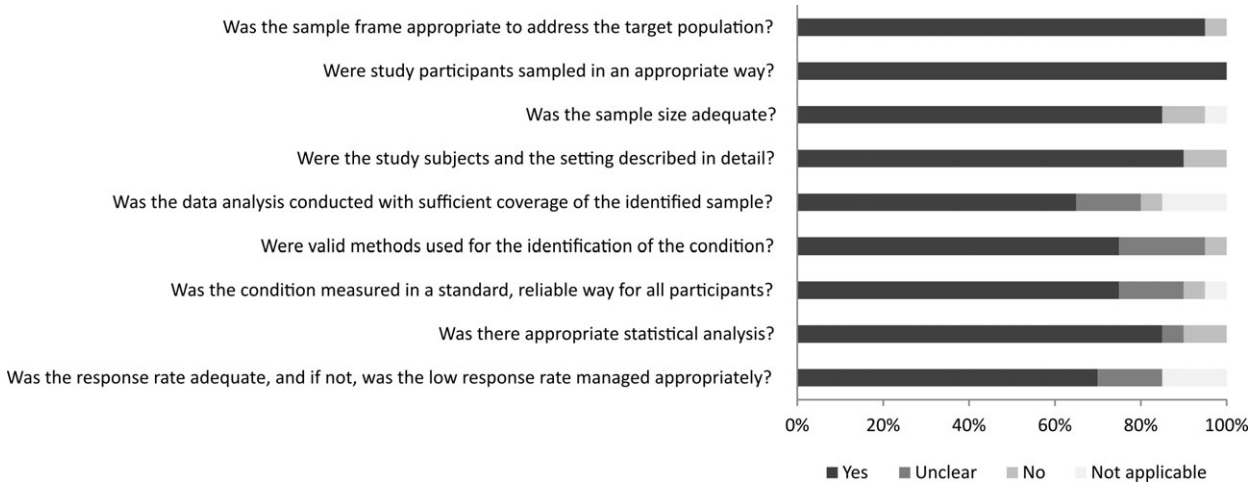


Figure 2 Results of the methodological quality item assessment presented as percentage among all included studies.

Worth mentioning that CHD (POR = 16.4, $p < 0.001$) was the disease with the highest odds ratio between all. Fig. S2 depicts the disease categorized meta-analysis in detail.

The studies result had considerable heterogeneity in CVID, SCID, and IgGSD subgroup analysis, substantial heterogeneity in SIgAD and agammaglobulinemia, moderate heterogeneity in CGD, DGS, WAS, and LAD, and finally no heterogeneity in AT, HIES, and CHS.

Discussion

We reported the parental consanguinity prevalence in format of three WHO regions based on 18091 individuals. As expected, parental consanguinity in patients with PID was dramatically high in Eastern Mediterranean region (65.7%), mostly due to high inbreeding rate in Middle East. When comparing Eastern Mediterranean region with Europe and Western Pacific, we observe a drastic decrease in consanguinity prevalence (5.6% and 2.3%, respectively). Regarding the similarities in ethnicity and social beliefs, we did not expect a considerable difference in consanguinity prevalence in the two groups. However, the prevalence of parental consanguinity in the North America is based on the data from one study arising from a single national referral center in Mexico and cannot be representative for the Americas.

We found that offspring of consanguineous marriages were more likely to suffer from a PID disease throughout life than the children with no parental consanguinity (Pooled POR: 3.0, 95% CI, 2.5–3.7). Although by reporting odds ratio we tried to match variables that could contribute to the prevalence of parental consanguinity in patients with PID (such as culture or geographic region) (32), we noticed a high degree of heterogeneity even in the pooled 'odds ratio'.

After pooling the data at the level of each disease, our findings followed a notable scheme. Among all the investigated diseases, those with AR pattern of inheritance had the highest level of prevalence odds ratio. The AR diseases alongside CGD were the only conditions with statistically significant POR. The other six diseases—although all with odds ratios greater than one—did not approve as statistically significant. The latter PID diseases fall into various inheritance patterns: WAS (X-linked); DGS (autosomal dominant); SIgAD, IgGSD, agammaglobulinemia, and CVID (Variable) (33).

There is a prevailing mentality that inbreeding increases the incidence of autosomal recessive disorders (ARDs). The rationale behind such hypothesis is that the chance of homozygosity boosts in the offspring of inbred couples, thus expressing the deleterious alleles (16). Several studies reported that ARDs are more common in communities with high consanguinity prevalence (34–36). The majority of these studies are geographically limited to specific regions of the world with high inbreeding rates and also cease at the level of reporting a difference in inbreeding rate rather than odds ratio (37).

We may declare with considerable confidence that there is a definitive high correlation between inbreeding and the likelihood of autosomal recessive PIDs. The odds ratios for AR PIDs were considerably higher than the mean pooled odds ratio for PIDs in general: SCID and AT (twofold); LAD (threefold), CHS (more than fivefold). The only exception here is HIES. The pooled POR for this disease was 2.9—close to the mean POR for PIDs. This observation may be understandable; as this particular disease has mainly a dual mechanism of inheritance based on the genotype, HIES may both follow an AR or an AD pattern (associated with DOCK-8 and STAT-3, respectively) (38, 39). We may assume that our sample of HIES cases included a combination of both genotypes of the disease.

Among diseases with other inheritance patterns, CGD was the only one that resulted in a significantly high odds ratio. CGD is mostly inherited as an X-linked trait (CYBB), and only about one-third of cases would be the autosomal recessive variants (associated with CYBA, NCF1, NCF2, and NCF4) (40); however, these epidemiologic statistics come from Western countries with low consanguinity prevalence. The data from high consanguine countries demonstrate the

Table 1 Detailed characteristics of the studies included in the systematic review

Study	Country	Year	N*	Type	Quality	Study CP† (%)	Population CP	POR‡ (95% CI)
The Americas								
Reyes et al. 2015 (16)	Mexico	1991–2012	161	Mixed	High	11.2	1.27% (43)	9.79 (5.93–16.17)
Europe								
Marschall et al. 2015 (19)	Swiss	2008–2014	348	Mixed	High	2.3	N/A	N/A
CEREDIH 2010 (23)	France	2005–2009	3083	Mixed	High	15	0.8% (45)	21.86 (19.71–24.24)
Gathmann et al. (18) 2013	Germany	1963–2010	917	Mixed	High	8.6	N/A	N/A
Kilic et al. 2013 (26)	Turkey	2004–2010	1130	Mixed	High	14.3	22% (46)	0.59 (0.49–0.70)
Gathmann et al. 2012 (11)	Europe	Up to 2011	13708	Mixed	High	8.8	4.8% (45–50)	1.92 (1.72–2.16)
Edgar et al. 2014 (27)	The UK§	2008–2012	924	Mixed	High	2.9	0.4% (51)	6.91 (2.43–19.67)
Eastern Mediterranean								
Reda et al. 2009 (52)	Egypt	2004–2008	64	Mixed	Mod¶	62.5	28.96% (53)	4.09 (2.46–6.78)
Rezaei et al. 2006 (54)	Iran	1980–2006	930	Mixed	High	68.5	38.6% (55)	3.46 (3.01–3.97)
Aghamohammadi et al. 2014 (25)	Iran	2006–2013	731	Mixed	High	63.1	38.6% (55)	2.72 (2.34–3.16)
Al-Herz et al. 2012 (24)	Kuwait	2004–2011	176	Mixed	High	78	54.3% (56)	3.06 (2.12–4.39)
Bousfiha et al. 2014 (21)	Morocco	1998–2012	421	Mixed	Mod	43.2	19.9% (57)	3.06 (2.50–3.76)
Al-Tamemi et al. 2012 (22)	Oman	2005–2010	90	Mixed	Mod	81	56.3% (58)	3.33 (2.50–3.76)
Ehlayel et al. 2013 (17)	Qatar	1998–2012	131	Mixed	Mod	61.1	54% (59)	2.07 (1.36–3.14)
Al-saud et al. 2015 (60)	KSA**	2010–2013	502	Mixed	High	75	56% (61)	2.34 (1.91–2.88)
Mellouli et al. 2015 (20)	Tunisia	2002–2003	710	Mixed	High	58.2	26.9% (62)	3.78 (3.22–4.44)
Western Pacific								
Yee et al. 2008 (28)	Australia	1995–2001	33	SCID††	High	22	0.23% (4)	116.68 (49.85–273.10)
Wang et al. 2011 (31)	China	2004–2009	195	Mixed	Mod	2	1.9% (63, 64)	1.06 (0.39–2.88)
Lee et al. 2011 (65)	China	2001–2011	272	Mixed	Mod	<3	1.9% (63, 64)	1.37 (0.64–2.92)
Hayakawa et al. 1985 (29)	Japan	Up to 1984	84	CGD‡‡	Mod	3.6	3.9% (66)	0.91 (0.29–2.90)
Nagai et al. 2013 (30)	Japan	2000–2010	15	CHS§§	High	13	3.9% (66)	3.79 (0.85–16.85)

*Sample size.
†Consanguinity prevalence.
‡Prevalence odds ratio.
§The United Kingdom.
¶Moderate.
**Kingdom of Saudi Arabia.
††Severe combined immunodeficiency.
‡‡Chronic granulomatous disease.
§§Chediak-Higashi syndrome.

dominance of autosomal recessive cases regarding prevalence rates (41, 42). Although the odds ratio reached statistical significance, POR of 2.7 was relatively low compared to the other significant odds ratios in ARDs, which can be explained by the duality of CGD inheritance pattern.

Our results also confirm the evidence that suggests that impact of consanguinity on monogenic disorders is disproportionate to the prevalence of the disorder in the population (43). As depicted in S2, the highest odds ratio belongs to CHS—the rarest disease in our study—followed by LAD.

There was significant heterogeneity in the prevalence of consanguinity, and also in the prevalence odds ratios (POR). Apart from geographic and ethnic diversities, the use of different definitions of consanguinity by the studies and variations among registration systems are possible explanations. We also noted variations in the PORs among PIDs with AR inheritance pattern (such as CHD, LAD, or SCID). Different genetic background in different ethnicities explains a part of these variations. For example, it seems that there are common ancestors with same mutations for RAG1 and RAG2 in some regions of Middle East. Al-Herz et al. (44) demonstrated that deficiencies in RAG1, RAG2, and MHC II (AR traits) are the main origin of CID in Middle Eastern nations like Kuwait; whereas in Western countries, the X-linked SCID is more prevalent due to common gamma chain (yc) deficiency. It is competent to put this finding down to consanguinity being more common in the Middle East. We should also mention the fact that not all the PID cases have been registered in the studies. The lack of perfect registration systems especially leads to discrepancies among the ORs of the rarest PIDs—such as the AR-inherited immunodeficiencies.

The estimated pooled mean of age at onset in this study was 43.6 months (95% CI: 36.9–50.4). Although data of age at diagnosis were incomplete, it did not show any trend among different geographic regions. Previously Gathmann et al. (11) reported that diagnostic delay (time period between the onset

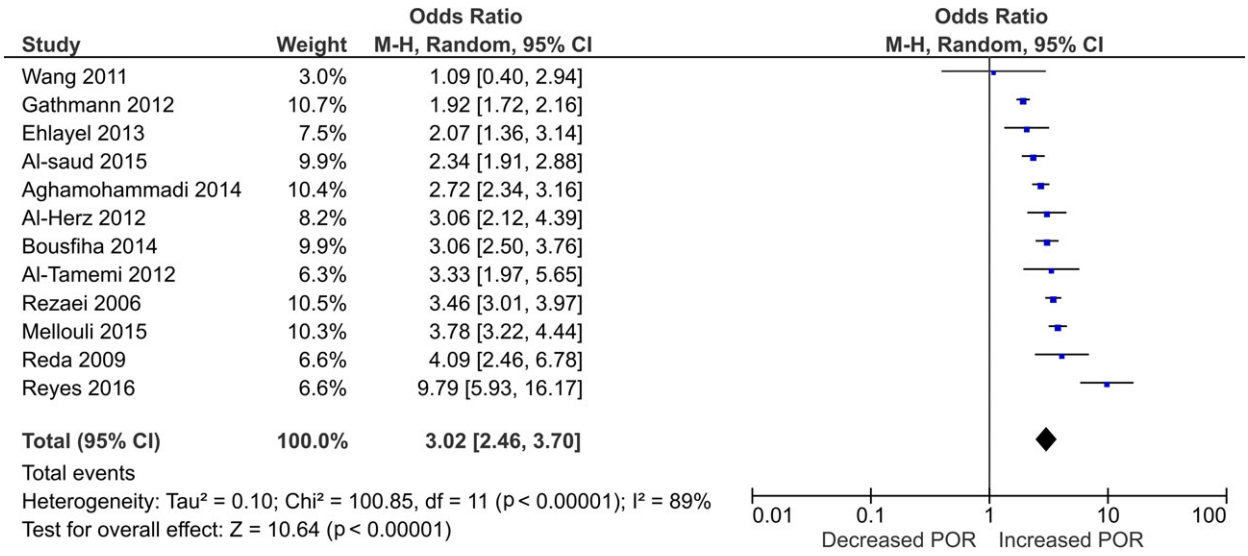


Figure 3 Estimated prevalence odds ratio (POR) of parental consanguinity in patients with primary immunodeficiency diseases.

of disease and the diagnosis) has been decreased for IgG subclass deficiency and agammaglobulinemia from 1987 to 2010. Longitudinal studies with large sample sizes are needed to investigate the trend of diagnostic delay through time and geographic regions.

To the authors' knowledge, this is the first systematic review and meta-analysis assessing parental consanguinity in patients with PID and in the matched general population. We hope that genetic counselors, health educators, and consanguineous couples seeking preconception counseling, all over the world, benefit from the results of this systematic review and meta-analysis.

A limitation of the present meta-analysis was that most of the included articles did not define 'consanguinity', and even those who defined were not using a unique definition. So, the prevalence of parental consanguinity and the odds ratios may have been underestimated or overestimated. Probable imperfections of data registry systems can be the other important limitation of this review.

With this systematic review, we manifested that odds of consanguinity are threefolds in parents of patients with PID compared to the normal healthy population. We also benefited from meta-analyzing the available data and displayed the magnitude of inbreeding influence on the 12 globally most common PID diseases. The analysis revealed that impact of consanguinity only kicks in when dealing with autosomal recessive PID diseases—or those with a dominant autosomal recessive side.

Acknowledgments

We would like to thank Seyed-Mohammad Fereshtehnejad and Somayye Barati for comments and statistical advice that significantly improved the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of the 12 most prevalent primary immunodeficiency subtypes included in the additional meta-analysis.

Figure S2. Estimated prevalence odds ratios (POR) of parental consanguinity in patients with different subtypes of primary immunodeficiencis included.