Original Article

Association Between Wilson Disease and Parental Consanguinity in Bangladesh: A Meta-Analysis

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ABSTRACT

Objective

This study aims to compare the prevalence of Wilson's disease (WD) among individuals born to consanguineous marriages versus those born to non-consanguineous unions in Bangladesh.

Materials and methods

Several databases, including Web of Science, PubMed, Scopus, and Google Scholar and Bangla JOL were searched using relevant keywords. Eligible studies were those conducted in Bangladesh that reported either the number or percentage of parental consanguinity among patients with WD. Pooled prevalence and 95% confidence intervals (CIs) were calculated. Publication bias was assessed and sensitivity analysis was conducted.

Results

A total of 334 articles were initially identified, of which thirteen studies were ultimately included in the analysis. Findings demonstrated that 29.8% of WD patients were born to consanguineous parents (pooled event rate = 0.298, 95% CI = 0.24–0.35; I^2 = 48%), while 70.2% were born to non-consanguineous parents (pooled event rate = 0.702, 95% CI = 0.65–0.76). These findings suggest that most WD cases in Bangladesh occurred in non-consanguineous families. Both Egger's test (p=0.23) and Begg and Mazumdar's test (p=0.12) suggested the absence of publication bias.

Conclusion

The results show that parental consanguinity does not significantly increase the risk of WD in people from Bangladesh.

Keywords

Wilson disease; Bangladesh; consanguineous marriages; prevalence

INTRODUCTION

WD is a rare autosomal recessive disorder (ARD) caused by inheriting mutations in the *ATP7B* gene from both parents[1]. In ARD, a person receives two copies of a mutated gene, one from each parent, who are usually carriers[2]. The *ATP7B* gene is found on chromosome 13q14.3 and is about 80 kb long, with 20 introns and 21 exons[3]. The gene is mainly expressed in the liver, but also in the kidney, placenta, brain, lungs, and mammary glands[3]. It encodes a P-type ATPase that facilitates copper transport, mainly in the trans-Golgi network of liver cells, and is important for keeping copper levels balanced in the liver[4,5]. Copper is an essential trace element needed for several enzymes involved in respiration, iron metabolism, melanin and neurotransmitter production, antioxidant defense, and connective tissue development[6]. Copper from food is absorbed in the duodenum and carried to the liver through the blood. The liver is the main organ for copper metabolism, balancing copper through absorption from the intestine and excretion in bile[7]. *ATP7B* facilitates the transport of copper into the secretory pathway by loading it onto ceruloplasmin. When copper levels in cells become too high, *ATP7B* moves the extra copper into bile for removal, which prevents toxic buildup[8]. Mutations in *ATP7B* reduce

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ceruloplasmin production and impair the excretion of copper into bile. This leads to copper building up in the liver, causing toxicity[9]. Excess copper can enter the bloodstream and accumulate in other organs, especially in the brain, leading to neurological and psychiatric symptoms [1]. Liver involvement often starts without symptoms but can progress to hepatosplenomegaly, ascites, and variceal bleeding as signs of chronic liver disease. Some patients may develop acute liver failure, a severe form of WD, characterized by jaundice, hepatitis, an enlarged liver, and blood clotting problems, sometimes accompanied by encephalopathy[10]. Tremor, dystonia, and parkinsonism are the most common neurological symptoms. Psychological symptoms can include anxiety and depression, as well as psychosis and disruptive behavior[11]. WD can affect people of any age, but it is usually diagnosed before age 40, most commonly between 5 and 35 years[12]. Worldwide, WD is uncommon, affecting about one person in 30,000 to 40,000. Carriers are more common, about one in every 90 people[13,14]. WD can be caused by over 700 variants, but the types vary by region. In European and American groups, H1069Q is the most common variant, found in 50–80% of cases [15,16], while in East Asian populations, R778L is more common, seen in 14–49% of cases[17,18]. Consanguinity is often assumed to increase WD risk[19]; but no meta-analysis has been done yet. Consanguinity refers to relationships between partners who are second cousins or more closely related [20]. About 20% of people worldwide live in areas where consanguineous marriages are common[21]. The rate of these marriages is influenced by factors like religion, culture, and geography[22]. These factors have led to higher rates of consanguinity in South Asia, the Middle East, and North Africa[23]. Bangladesh is one such region, although there is limited data on the prevalence of consanguinity and its health effects[24]. Several studies conducted in Bangladesh have reported the prevalence of WD among individuals from consanguineous families[25,26,27,28]. The present meta-analysis aims to compare the prevalence of WD among offspring of consanguineous and non-consanguineous marriages in Bangladesh.

METHODS AND MATERIALS

Literature search

A systematic search was conducted on two occasions: first on June 14, 2024, and an updated search on August 14, 2025, using the databases Web of Science, PubMed, Scopus, Google Scholar, and BanglaJOL. For Web of Science, PubMed, and Scopus, the search strategy included the following keywords: (((Bangladesh)) AND ((Wilson's disease) OR (Wilson disease) OR (Hepatolenticular degeneration) OR (progressive lenticular degeneration))). For Google Scholar, the terms used were: "Bangladesh," "Wilson's disease," "Wilson disease," "Hepatolenticular degeneration," and "progressive lenticular degeneration." For BanglaJOL, the search included: ((Wilson's disease) OR (Wilson disease) OR (Hepatolenticular degeneration) OR (progressive lenticular degeneration)). In addition, the reference lists of the included articles were screened for relevant studies. The study was conducted following the PRISMA guidelines.

Inclusion & exclusion criteria

The inclusion criteria for this study were as follows: (i) patients diagnosed with WD; (ii) studies conducted in Bangladesh; (iii) studies that reported parental consanguinity or non-consanguinity among Wilson's disease patients, expressed as numbers or percentages; and (iv) original research. Exclusion criteria were non-English articles, case reports, reviews, theses, conference abstracts, animal studies, and articles for which the full text was unavailable.

Data extraction

Two authors independently searched the literature and extracted data from the included articles. The following data were extracted: first author, publication year, study location, number of WD patients, and the number or percentage of consanguineous and non-consanguineous patients.

Statistical Analysis

The Comprehensive Meta-Analysis program was used to conduct statistical analyses. The overall prevalence and corresponding 95% CIs were estimated, and a random-effects model was applied. Heterogeneity among studies was assessed using the Q statistic (based on the χ^2 test) and the I^2 statistic. A high level of heterogeneity was defined when $I^2 > 50\%$. Publication bias was evaluated by inspecting funnel plots, as well as Begg and Mazumdar's rank correlation test and Egger's regression test; $p<0.05$ indicates the presence of publication bias. The robustness of the results was assessed through sensitivity analysis.

RESULTS

Study selection

A total of 334 articles were identified from various databases: PubMed (n = 93), Web of Science (n = 7), Scopus (n = 11), Google Scholar (n = 174), and BanglaJOL (n = 49). After manually removing 79 duplicate records, the titles, abstracts and full texts of the remaining 255 articles were screened. Finally, 13 articles met the inclusion criteria and were included in the analysis. The reasons for excluding the 242 articles were as follows: 18 case reports, 20 reviews, 21 non-English articles, 4 books, 4 articles with unavailable full texts, and 175 irrelevant studies. Table 1 summarizes the features of the included studies, and Figure 1 shows the flow of article selection.

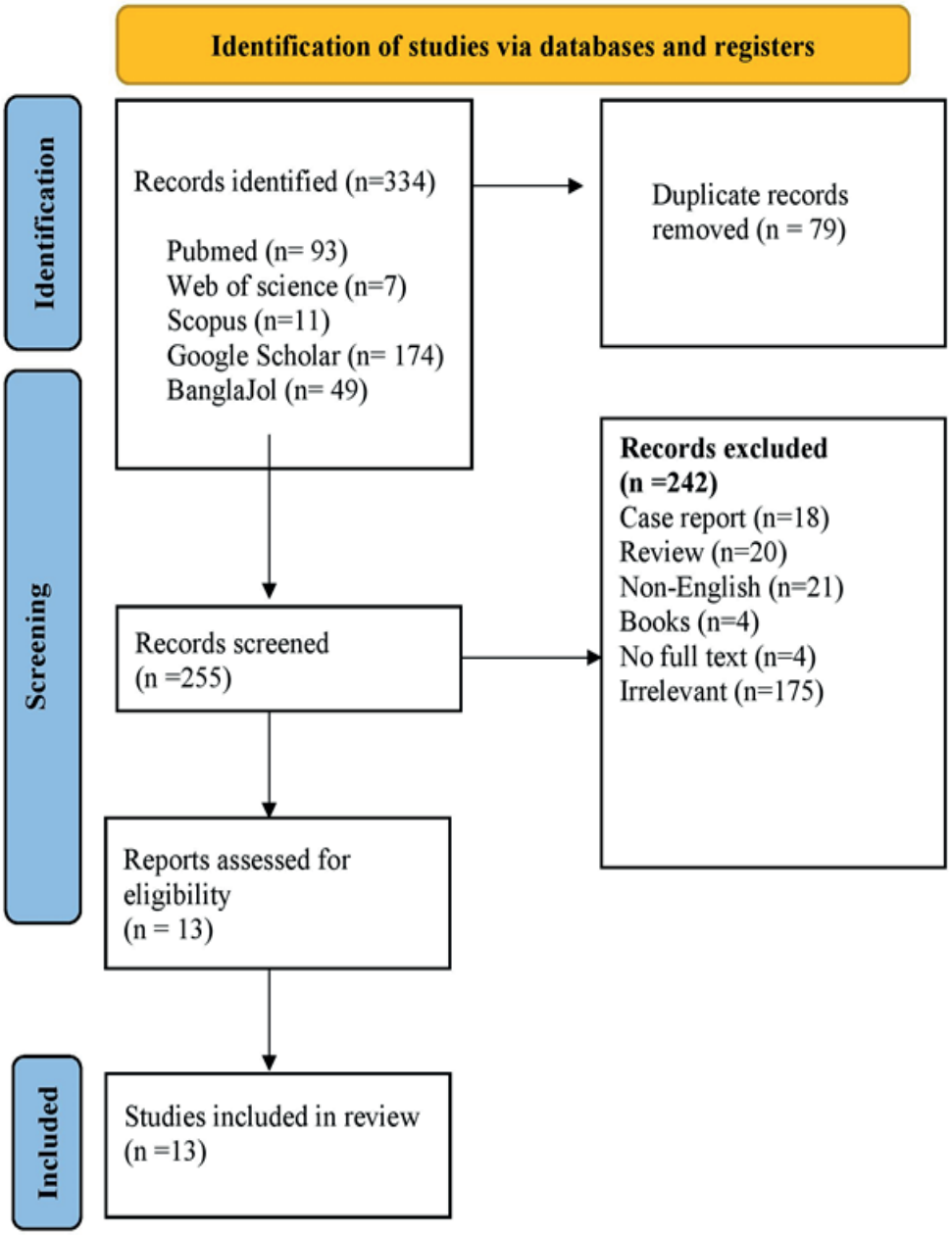

Figure 1: Flowchart for the Article Search Process

Table 1: Features of the included studies

References	Study duration	Place of Study	WD Patients (Number)	Consanguinity (number)	Consanguinity (%)	Non-consanguinity
[25]	2015-2018	BSMMU	40	13	34.2%	27
[27]	2017-2018	BSMMU	37	9	24%	28
[28]	2010 -2011	BSMMU	30	16	53.3%	14
[29]	2011-2013	BSMMU	100	30	30%	70
[30]	2014-2019	Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh	60	23	38.3%	37
[31]	2019 -2021	BSMMU	27	06	22.2%	21
[32]	1995 -2004	BSMMU	32	4	12.5%	28
[33]	2007- 2008	Dhaka Medical College Hospital	16	7	44%	9
[34]	2008 -2010	BSMMU	31	8	25.8%	23
[35]	2018-2019	BSMMU	27	11	40.7%	16
[36]	2015-2020	Department of Paediatric Neurology, BSMMU	45	9	20.0%	36
[37]	2015-2018	Pediatric Gastroenterology and Nutrition, BSMMU	42	13	30.9%	29
[38]	2018-2021	Department of Paediatric Neurology, BSMMU	74	15	20%	59

BSMMU: Bangabandhu Sheikh Mujib Medical University

Association of Parental marriage & Wilson disease

Meta-analysis indicated that 29.8% of patients with WD were born to consanguineous parents (pooled event rate = 0.298, 95% CI = 0.24, 0.35), while the remaining 70.2% were born to non-consanguineous parents (pooled event rate = 0.702, 95% CI = 0.65, 0.76). The observed heterogeneity (I^2 = 48%) was not statistically significant. Sensitivity analysis did not identify any individual study that significantly influenced the pooled results. The funnel plot (figure 3), Begg and Mazumdar's rank correlation test (p = 0.251) and Egger's test (p = 0.318) indicated that no significant publication bias was observed. Subgroup and meta-regression analyses were not performed due to a low level of heterogeneity. The pooled estimates remained unchanged after applying the Trim and Fill method.

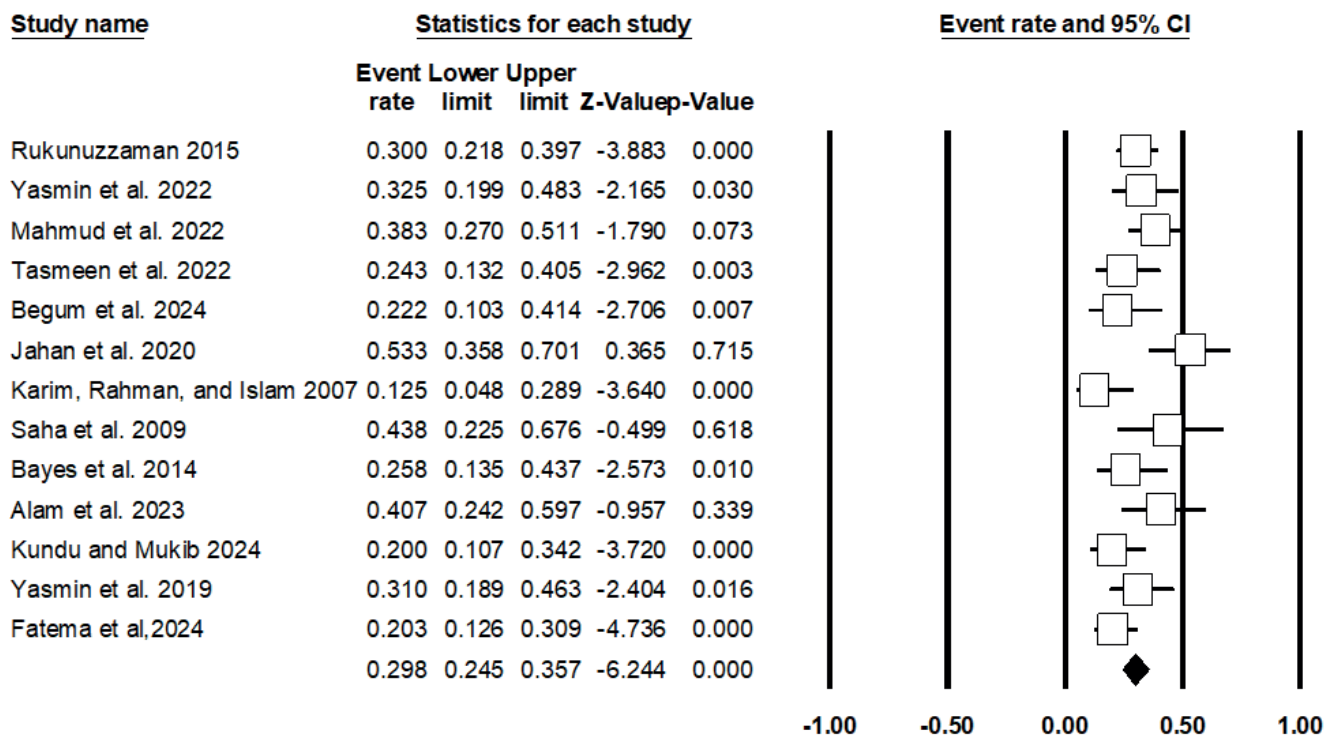

Figure 2: The forest plot illustrates the pooled prevalence of Wilson disease among individuals with parental consanguinity.

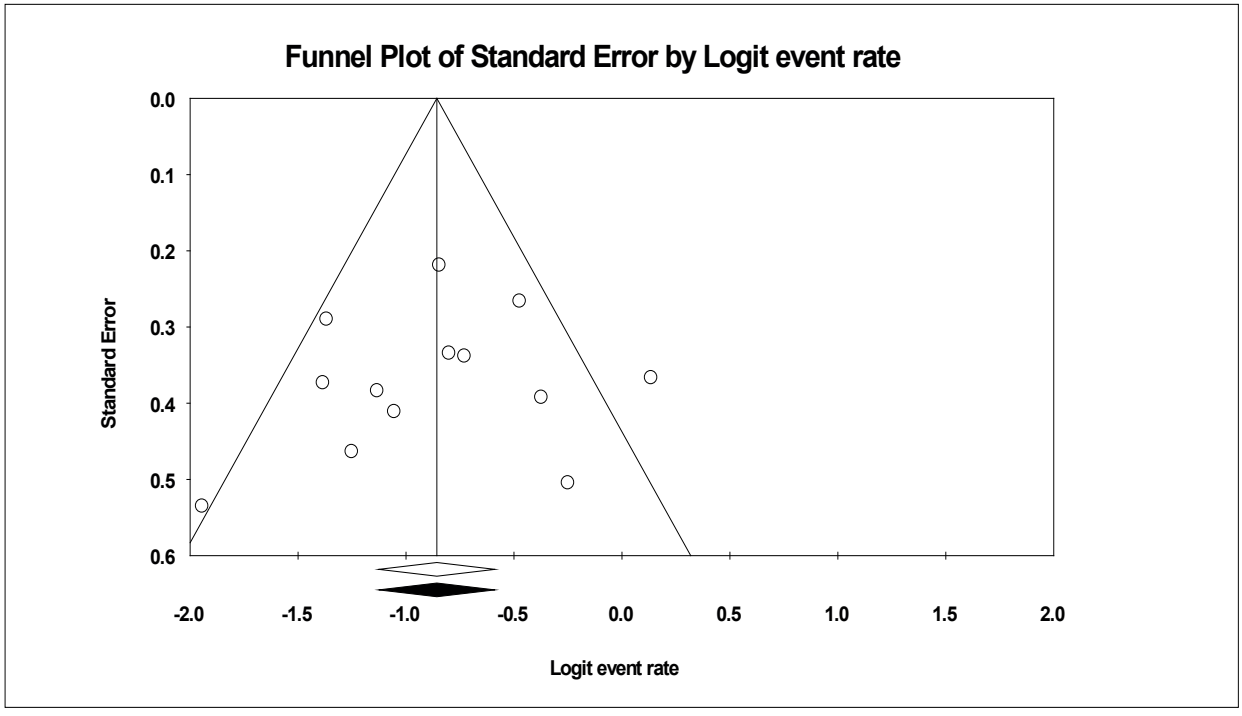

Figure 3: The funnel plot demonstrates evidence of symmetry, suggesting no publication bias.

DISCUSSION

A gene mutation is a permanent change in the DNA sequence that occurs when cellular repair mechanisms fail to correct DNA damage or replication errors[39]. Mutations can happen because of mistakes during DNA replication or problems with DNA repair. They can also be caused by environmental factors like radiation or by chemical agents[40]. Mutations that occur in somatic cells, which do not pass to offspring, are referred to somatic mutations[41], while mutations in the germ cell lineage (i.e., sperm and egg) that can be transferred to offspring are known as germline mutations[42]. WD is an example of a genetic disorder caused by germline mutations[43]. It is usually diagnosed by measuring low serum ceruloplasmin and high copper levels, but genetic testing of the *ATP7B* gene is becoming more important, especially when biochemical tests are unclear[44]. WD is usually treated with oral chelators like penicillamine and trientine, zinc for maintenance, and tetrathiomolybdate is still being studied[45]. Despite advancements in treatment, knowledge of the genetic epidemiology of WD is still essential for directing family counseling and early diagnosis. Evaluating the prevalence of WD among consanguineous and non-consanguineous parents is crucial, as mutated genes can be passed from parents to their offspring. This study represents the first meta-analysis evaluating the prevalence of WD in the context of consanguineous marriages. Our analysis revealed that 29.8% of WD patients were born to consanguineous parents, whereas 70.2% were born to non-consanguineous parents, indicating that the risk of WD is not confined to consanguineous unions. This highlights the importance of considering WD in all populations, regardless of parental relatedness, and emphasizes the need for broader genetic screening. Consanguinity rates are significantly higher in Arab countries compared to non-Arab countries, whereas WD prevalence appears greater in non-Arab countries[46]. In South Asia, consanguineous marriages are more frequent than in the United States, but the rate of WD is similar, at about 10 to 12 cases per 100,000 people[47,48]. In France (carrier frequency 1/31; consanguinity 2.6%) and Britain (carrier frequency 1/25; consanguinity 1.1%), WD is primarily associated with the relatively high carrier frequency of *ATP7B* mutations, while the contribution of consanguinity is minimal due to its low prevalence[49,50]. In Bangladesh, the prevalence of consanguineous marriage is 6.64%[51], but the carrier frequency of *ATP7B* mutations has not yet been evaluated. Higher numbers of WD cases among non-consanguineous parents have been observed[31,32], which may be due to the higher worldwide carrier frequency of *ATP7B* mutations[52]. Instead, high carrier frequencies likely contribute substantially to disease occurrence, and the underlying reasons for these high frequencies warrant further investigation. The included studies focus exclusively on symptomatic or severe cases of WD, as all were conducted in hospital-based settings. Therefore, these samples do not accurately reflect the general population. To better understand the broader epidemiological context, population-wide genomic studies or community-based research are needed. Future research could assess the *ATP7B* gene carrier frequency among relatives and non-relatives. This would help clarify the link between WD and consanguinity. Moreover, the included studies did not specify whether the parents were first-degree or second-degree cousins that should be addressed in future research. Additionally, most of the included studies (11 out of 13) were conducted at the same center (BSMMU), raising the possibility of overlapping patient populations. This overlap could bias the findings. Future research should carefully address and avoid potential patient overlap. Based on the current evidence, parental consanguinity alone may not be a significant risk factor for WD in Bangladesh.

CONCLUSION

Parental consanguinity does not appear to be a major determinant of WD in Bangladesh. Implementing population-based carrier screening for *ATP7B* mutations is necessary to identify individuals at risk for WD and to decrease its prevalence within the national population.

Statements & Declarations

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The authors have no relevant financial or non-financial interests to disclose.

Conflict of interest

The authors have no conflicts of interest.

Ethical Statement

None to be declared.

Authors' Contribution

Conception, Writing original draft & Data extraction: Md. Mojahidur Hasan & Sehreen Tory; **Software, Statistical analysis, Review & Editing, Validation:** Md. Mojahidur Hasan, Sehreen Tory, Hamdi Gokahmetoglu; **Review & Editing:** Yusuf Tutar

Data sharing: Data sharing is not applicable.

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