

# Male Factor Infertility and Risk of Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis

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## Abstract

**Objective:** Multiple sclerosis is an autoimmune disease of central nervous system (CNS). There are a few articles studying the risk factors of developing MS in men. Male infertility can stem from a range of etiological factors such as genetics or environment. In the context of MS, research suggests a potential link, possibly due to shared immunological and inflammatory mechanisms. Therefore, we designed this study to evaluate the relationship between male infertility and MS development.

**Materials and methods:** We systematically searched PubMed, Embase, Scopus, web of science, Google scholar and gray literature including references of the references as well as conference papers which were published up to June 2021. The search strategy in PubMed was ("Infertility, Male"[Mesh] OR [Male Infertility] OR [Sterility, Male] OR [Male Sterility] OR [Subfertility, Male] OR [Male Subfertility] OR [Sub-Fertility, Male] OR [Male Sub-Fertility] OR [Sub Fertility, Male]) AND ("Multiple Sclerosis"[Mesh] OR [Sclerosis, Multiple] OR [Sclerosis, disseminated] OR [Disseminated Sclerosis] OR [MS] OR [Multiple Sclerosis, Acute Fulminating]) AND ("Testicular Diseases"[Mesh] OR [Disease, Testicular] OR [Diseases, Testicular] OR [Testicular Disease]) AND ("Multiple Sclerosis"[Mesh] OR [Sclerosis, Multiple] OR [Sclerosis, disseminated] OR [Disseminated Sclerosis] OR [Multiple Sclerosis, Acute Fulminating] OR [MS]).

**Results:** The literature search revealed 197 articles, after deleting duplicates 109 remained. For the meta-analysis, 3 studies were included. Totally, 2090 MS cases as well as 3895562 healthy subjects were enrolled. One hundred and fourteen infertile men were in MS group and 139716 infertile men were in controls. The pooled OR for male factor infertility and odds of developing MS was 1.87 (95% CI: 0.89-3.94) ( $I^2=86.1%$ ,  $P=0.001$ ).

**Conclusion:** The results of this systematic review and meta-analysis show that there is no relationship between male factor infertility and risk of MS.

**Keywords:** Multiple Sclerosis; Infertility; Risk



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## Introduction

Multiple sclerosis, an autoimmune disease of central nervous system (CNS), characterized by axonal demyelination and a wide categories of physical and psychological complications (1, 2).

The exact etiology is unknown and both genetics and environment have been considered to have roles in developing the disease (3). The disease is more prevalent in women and sex hormones are considered to play role (4). Age at menarche, oral contraceptive pills(OCP) use, pregnancy history, and number of parties are among possible contributing factors (5). The disease remit during pregnancy and worsens after delivery (6). The disease onset is later but the progression is more rapid and prognosis is poorer (7, 8).

Contrary to number of studies for risk factors of developing MS in women, there are little studies or male cases. Male infertility can stem from a range of etiological factors, including genetic abnormalities, hormonal imbalances, anatomical anomalies, and lifestyle factors such as smoking and excessive alcohol consumption. The incidence of male infertility varies widely, with estimates suggesting that around 7% of men experience infertility globally. In the context of MS, research suggests a potential link, possibly due to shared immunological and inflammatory mechanisms (9). A previous study showed that endogenous testosterone level is lower in men with MS while the other study demonstrated that male factor infertility is a risk factor of developing MS in men (4). However, more research is needed to establish a definitive connection between these two conditions and to uncover the underlying mechanisms that may contribute to their association. Therefore, we designed this study to evaluate the relationship between male infertility and MS development.

## Materials and methods

Gilbert and colleagues developed the BCI questionnaire at the University of Michigan in 2004 (8). We transl We systematically searched Pubmed, Embase, Scopus, web of science, Google scholar and gray literature including references of the references as well as conference papers which were published up to October 2022.

Inclusion criteria: cohort or case control studies, articles providing crude odds ratio of infertility or

hypofunctional testis and MS.

Exclusion criteria: cross sectional, and review articles.

**Search strategy:** The search strategy in PubMed was ("Infertility, Male"[Mesh] OR [Male Infertility] OR [Sterility, Male] OR [Male Sterility] OR [Subfertility, Male] OR [Male Subfertility] OR [Sub-Fertility, Male] OR [Male Sub-Fertility] OR [Sub Fertility, Male]) AND ("Multiple Sclerosis"[Mesh] OR [Sclerosis, Multiple] OR [Sclerosis, Disseminated] OR [Disseminated Sclerosis] OR [MS] OR [Multiple Sclerosis, Acute Fulminating]) AND ("Testicular Diseases"[Mesh] OR [Disease, Testicular] OR [Diseases, Testicular] OR [Testicular Disease]) AND ("Multiple Sclerosis"[Mesh] OR [Sclerosis, Multiple] OR [Sclerosis, Disseminated] OR [Disseminated Sclerosis] OR [Multiple Sclerosis, Acute Fulminating] OR [MS]).

Data regarding the name of the first authors, publication year, country, number MS cases, number of controls, and number with infertility were extracted.

**Quality assessment of study:** We assessed the risk of bias (quality assessment of each article) using the modified NEWCAS-TLE - OTTAWA QUALITY ASSESSMENT SCALE for (cohort studies) (10).

**Statistical analysis:** We used STATA Version 13.0 (Stata Corp LP, College Station, TX, USA) for data analysis. Random effects models were used and heterogeneity was determined by the inconsistency ( $I^2$ ) calculation.

## Results

The literature search revealed 197 articles, after deleting duplicates 109 remained. For the meta-analysis, 3 studies were included (Figure 1).

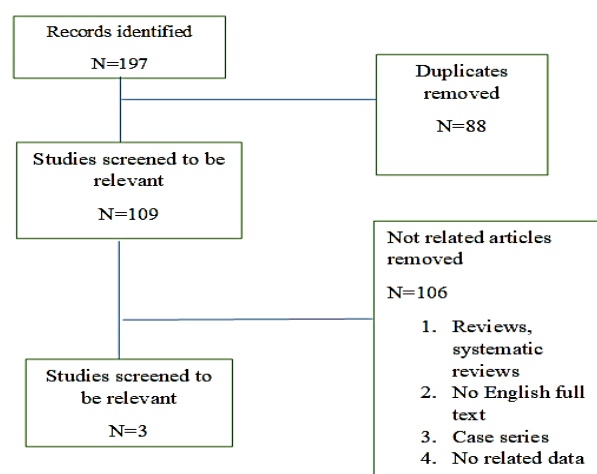


Figure 1: Flow diagram of including studies

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**Table 1:** Characteristics of included studies

First author	Published year	Country	Type of study	MS Cases (n)	healthy ones (n)	infertile men in cases (n)	infertile men in controls (n)	OR (95% CI)	Quality assessment
Brubaker	2017	USA	Cohort	228	363619	22	33055	1.07 (0.69-1.66)	6
Glazer	2017	Denmark	Cohort	85	50978	49	23962	1.5 (0.99-2.3)	6
Pakpoor	2014	United kingdom	Cohort	1745	3403304	11	5038	4.2 (2.3-7.7)	6

Three studies were included for final analysis. All of them were cohort studies, and 2090 MS cases as well as 3895562 healthy subjects were enrolled. One hundred and fourteen infertile men were in MS group and 139716 infertile men were in controls (Table 1).

The pooled OR for male factor infertility and odds of developing MS was 1.87 (95% CI: 0.89-3.94) ( $I^2=86.1\%$ ,  $P=0.001$ ) (Figure 2).

### Discussion

To our knowledge this is the first systematic review evaluating the odds of developing MS in men with infertility of hypo-functional testis. The results show that the odds of developing MS in men with infertility or hypo-functional testis is 1.68 (95% CI: 0.67-4.19), indicating that there is no association between male factor fertility status and developing MS.

In literature most evidences focus on developing autoimmune diseases in women with infertility and there is lack of evidence for men. Previous studies demonstrated that infertility and impaired semen quality were associated with development of diseases

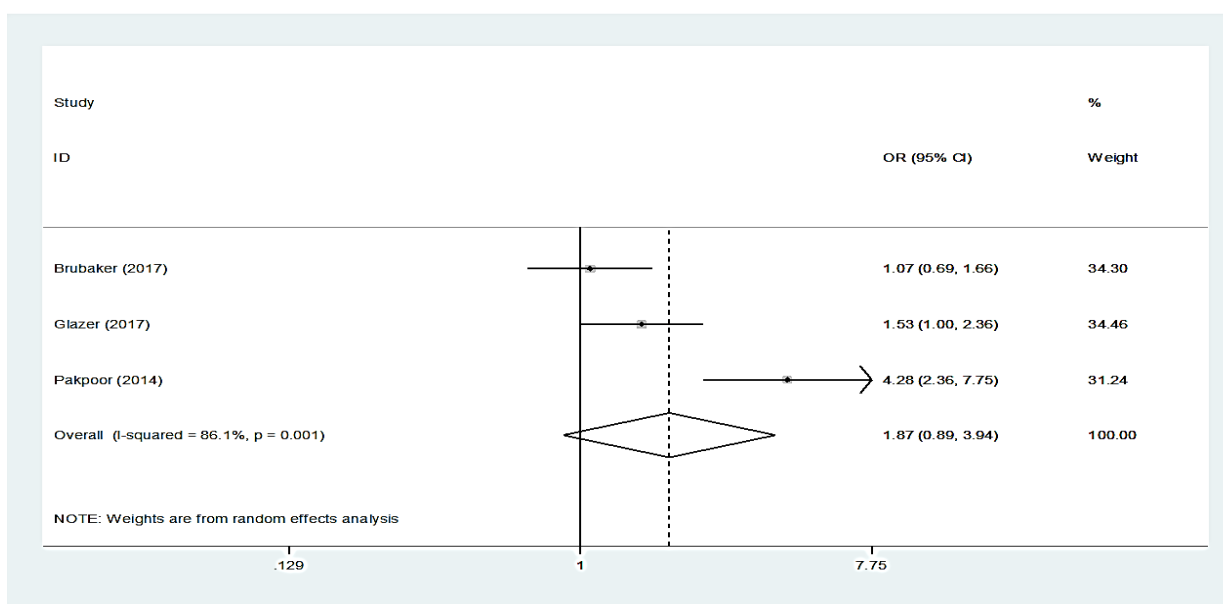
such as cancer, cardiovascular disease, diabetes as well as higher mortality rate (11-15).

Brubaker et al enrolled 33,077 infertile men and 330,770 healthy controls and reported the risk of developing MS as 1.18 (95% CI: 0.76–1.84). They found that infertile men had significantly higher risk of developing Hashimoto’s disease and psoriasis.

Glazer et al enrolled 85 MS men and 50978 healthy subjects. They found higher risk of developing MS in infertile men comparing with controls although the association was not significant (4).

Pakpoor et al found a significant strong association between MS and hypo-functional testis in men. They enrolled 1745 MS and 3403304 healthy controls (16).

There is a suggestion that interaction between immune, endocrine, and reproductive system results in developing infertility and autoimmune diseases (17). Androgens play an important role in developing autoimmune diseases and as we know the risk of autoimmune diseases is much more higher in females than males (18).



**Figure 2:** The pooled OR for male factor infertility and odds of developing MS

Sicotte et al administered transdermal testosterone in men with MS and found that cognition impairment and brain atrophy was lower in these men while the additional testosterone had no effects on brain lesions (19). On the other hand, it is shown that men with MS have lower level of endogenous testosterone and MS onset is associated with decreased level of testosterone levels(16, 20). Bove et al investigated that men with MS experience hypogonadotropic hypogonadism and lower testosterone levels were related with worse clinical outcomes (20).

Based on animal studies, testosterone has neuroprotective and anti-inflammatory role (21, 22) and Bobjer et al reported negative relationship between testosterone level and inflammatory markers (23).

A genetic linkage could be present between male factor infertility and MS as Montgomery et al found that children with MS had parents with impaired fertility and increased paternal age was associated with higher risk of MS (24).

All of these findings may support the role of testosterone and MS development while there is a need for large multi centric studies in various nations.

This systematic review and meta-analysis had some limitations. First, the number of included studies were limited. Second, in two studies infertility was assessed while in one hypo-functional testis. This shows gap of knowledge which could be solved by more original studies in this field.

## Conclusion

The results of this systematic review and meta-analysis show that there is no relationship between male factor infertility and risk of MS.

## Conflict of Interests

Authors declare no conflict of interests.

## Acknowledgments

None.

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