DOI: 10.18502/jfrh.v19i1.18433

Review Article

Does Age at Menarche Differ Between Patients With Multiple Sclerosis and Healthy Controls?: An Updated Systematic Review and Meta-Analysis

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Received June 2024; Revised and accepted March 2025

Abstract

Objective: Sex hormones play role in development of autoimmune diseases such as multiple sclerosis (MS). In our previous systematic review, we included three studies and reported the pooled odds ratio (OR) for increasing 1 year of age at menarche and risk of MS as 0.88. So, we designed this systematic review and meta-analysis to estimate the pooled mean age at menarche difference between women with MS and controls and also update the odds of developing MS by increasing age at menarche.

Materials and methods: We performed a comprehensive systematic search on PubMed, Scopus, EMBASE, and Web of Science on July 1st, 2023. Also, grey literature including conference abstracts and references of the references were investigated to find potentially relevant articles.

Results: A total 634 records were retrieved by systematic search. Also, one relevant record was identified from grey literature. After deduplication, 331 articles were remained for title/abstract screening and of those, 29 full-texts were evaluated. Finally, 15 studies were included in final analysis. The SMDs of age at menarche (control group – case group) ranged between -0.18 and 1.41. The pooled SMD of age at menarche (controls-cases) was 0.17 (95% CI: 0.09-0.25) ($I2=85.1\%$, $p<0.001$). OR for age at menarche and risk of MS ranged between 0.8 and 1.76, and the pooled OR for increasing 1 year of age at menarche estimated as 0.92(95% CI: 0.89-0.94) ($I^2=41.6\%$, $P=0.07$).

Conclusion: The results of this systematic review show that the mean age at menarche is higher in controls than women with MS, and the risk of MS decreases by increasing age at menarche.

Keywords: Multiple Sclerosis; Menarche; Risk

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), affecting mostly women in reproductive age, with a wide range of physical, and psychological complications (1, 2). The exact etiology is not determined, both genetics, and environmental factors play role in developing the disease (3).

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Before puberty, the incidence MS is similar in both sexes, while after puberty the incidence is higher significantly in females (4, 5). Sex hormones play a crucial role, and evidence show that strong activation of T-cells, and increased level of immunoglobulins mediate sex differences in MS (6, 7). On the other hand, during pregnancy MS activity is subsided, and after delivery disease activity flares up (8).

Delayed age at menarche, and pregnancy history are among protective factors of developing MS, while there are controversies regarding the use of OCPs and risk of MS (9).

In our previous systematic review, we included three studies and reported the pooled odds ratio (OR) for increasing 1 year of age at menarche and risk of MS as 0.88, indicating that each year increase of age at menarche, will result in 12% reduction of odds of developing MS (10).

As there are novel original articles discussing menarche age in MS patients, we intended to perform an updated systematic review and meta-analysis to estimate the pooled mean age at menarche difference between women with MS and controls and also update the odds of developing MS by increasing age at menarche.

Materials and methods

We reported this systematic review and meta-analysis based on PRISMA 2020 guideline (11).

Eligibility criteria

The inclusion criteria were: 1) all original studies that reported the menarche age in patient with multiple sclerosis and control ones.

The exclusion criteria were: 1) Letters to the editor 2) Original studies with no control group 3) Case reports 4) Case series

Information sources

We performed a comprehensive systematic search on PubMed, Scopus, EMBASE, and Web of Science on July 1st, 2023. Also, grey literature including conference abstracts and references of the references were investigated to find potentially relevant articles.

Search strategy

The search strategy of each database were designed using predefined keywords including:

((Menarche) OR (Pubert*)) AND ((Multiple Sclerosis) OR (Sclerosis, Multiple) OR (Sclerosis, Disseminated) OR (Disseminated Sclerosis) OR (Multiple Sclerosis, Acute Fulminating)

Selection process, and data collection

After conducting systematic search, all records were imported Endnote Version 21 and then, all duplicate studies were removed. Title/Abstract screening were performed by two independent researchers using Rayyan QCRI (https://www.rayyan.ai/) and potentially eligible articles were included in full text screening stage. In case of any disagreement, a third expert author were consulted. Extracted data were entered the Excel sheet by each one and checked by the third author.

Data items

Data extraction was conducted using a predefined table with following items: First author, publication year, country of origin, number of participants (Cases and controls), study design. Age at the time of study, age at MS onset, type of MS, and age at menarche.

Quality assessment

Two authors independently evaluated the quality of included studies using the Newcastle - Ottawa Quality Assessment Scale (12).

Statistical analysis: We conducted statistical analysis using STATA software Version 14.0 (Stata Corp LP, College Station, TX, USA). Inconsistency (I^2) was determined and in cases of $I^2 \geq 50\%$, random-effect model was used instead of fixed-effects model for meta-analysis. Effect size of age at menarche was determined and reported using standardized mean difference (SMD). In order to summary estimate, we calculated the pooled estimate and 95% CI to show certainty.

Results

A total 634 records were retrieved by systematic search. Also, one relevant record was identified from grey literature. After deduplication, 331 articles were remained for title/abstract screening and of those, 29 full-texts were evaluated. Finally, 15 studies were included in final analysis (Figure 1).

All included studies were case-control studies except one.

Four studies were from Iran, three from US, two from UK, two from Denmark, one from Japan, one from Canada, one from Norway, and one from Italy.

Studies were done between 2001 and 2020. A total of 11596 cases and 584449 controls were included in analysis. Adjusted OR for one year increase at age at menarche and MS development ranged between 0.49-1.76.The quality assessment scores of included studies were in range of 6 and 8 (Table 1).

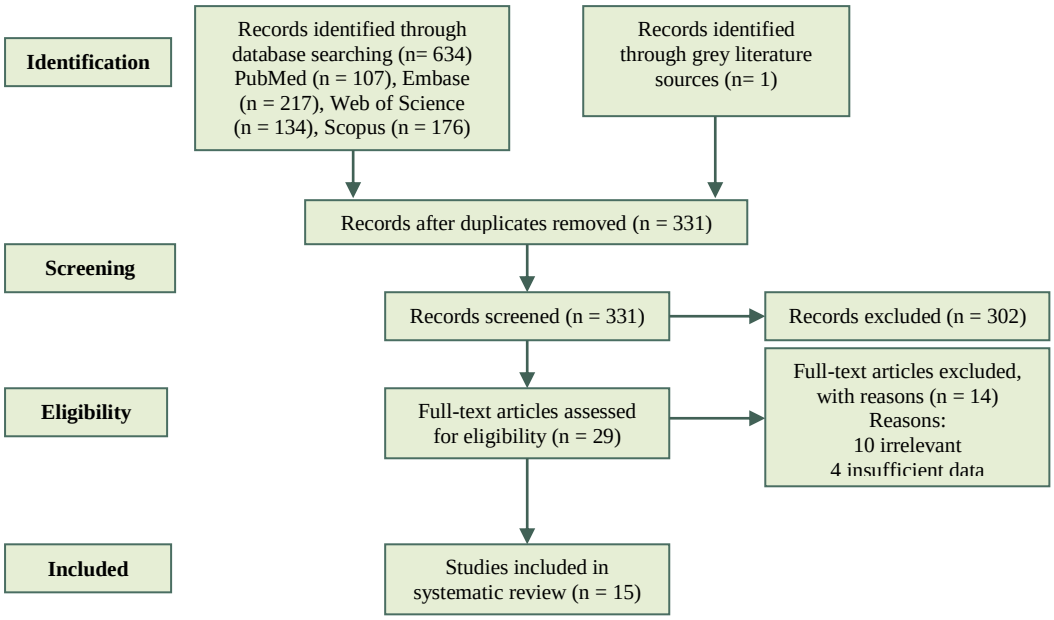

Figure 1: The flow chart of studies inclusion

The SMDs of age at menarche (control group – case group) ranged between -0.18 and 1.41.

The pooled SMD of age at menarche (controls-cases) was 0.17 (95% CI: 0.09-0.25) (I^2 = 85.1%, p<0.001) (Figure 2).

OR for age at menarche and risk of MS ranged between 0.8 and 1.76, and the pooled OR for increasing 1 year of age at menarche estimated as 0.92 (95% CI: 0.89-0.94) (I^2 = 41.6%, P=0.07) (Figure 3).

Discussion

This systematic review and meta-analysis is the update of our previous study.

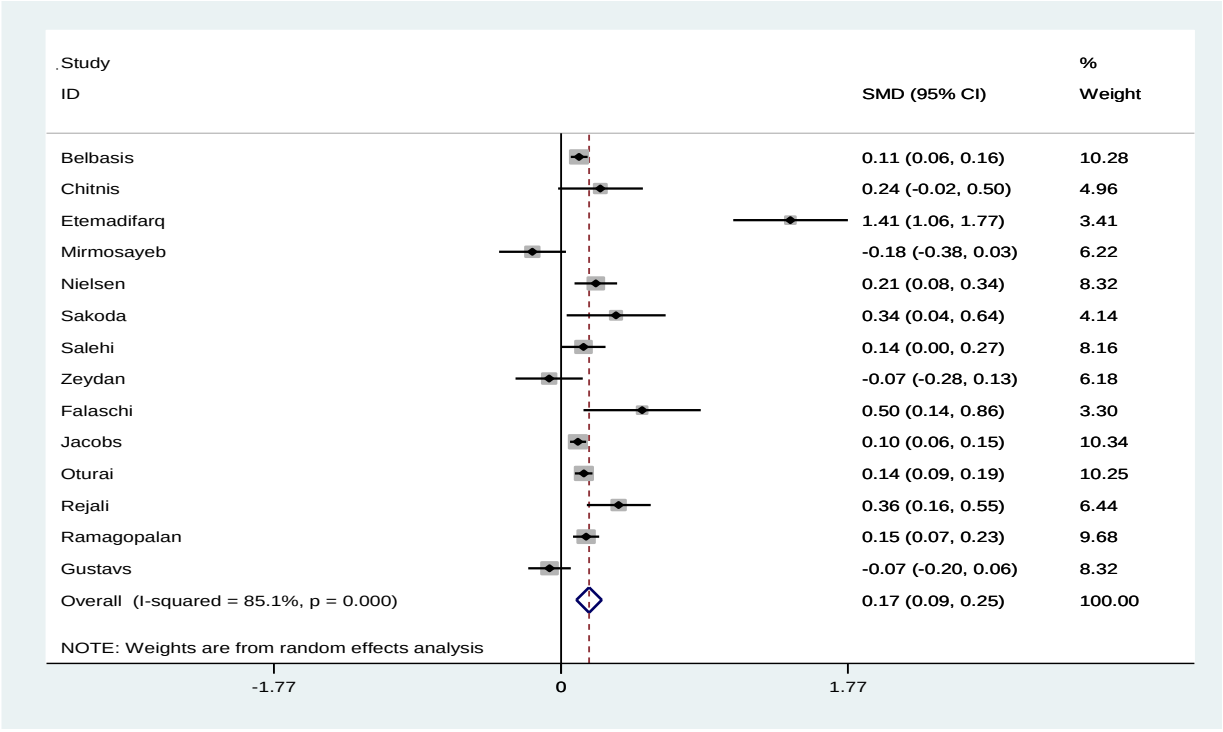

Figure 2: The pooled SMD of age at menarche

Table 1: Basic characteristic of included studies

Author	Year	Country	Study design	Participants	Age	Age at menarche	Age at MS onset	Type of MS	Adjusted OR	Crude OR	Quality assessment
Belbasis et al.	2019	UK	Case control	1418 cases, 235977 controls		Case: 12.77±1.66 Control: 12.95±1.61			0.931 (0.900,0.962) one-year increase		8/9
Chitnis et al.	2016	US	Case control	83 cases, 181 controls		Case: 11.6± 1.3 Control: 11.9± 1.2		All pediatric MS	0.97 (0.75,1.26) one-year increase	0.83 (0.65-1.05)	7/9
Etemadifar et al.	2017	Iran	Case control	77 cases, 77 controls		Case: 12±1 Control: 13±0			1.76 (0.60, 5.12) one-year decrease		8/9
Mirmosayeb et al.	2018	Iran	Case control	181 cases, 182 controls	Case: 36.04 ±9.86 Control: 35.16± 11.30	Case: 13.59±1.87 Control 13.29±1.53					6/9
Nielsen et al.	2016	Denmark	Cohort	226 cases, 77104 controls	29.9± 4.3	Case: 13.0 ±1.5 control: 13.3± 1.4			0.89 (0.81–0.98)		8/9
Sakoda et al.	2019	Japan	Case control	80 cases, 88 controls		Case: 12.4 ± 1.46 / Control: 12.9 ± 1.48			0.80 (0.65, 0.99) one-year increase		7/9
Salehi et al.	2018	Iran	Case control	399 cases, 541 controls	Case: 30.64 ±7.58 Control: 31.73 ±9.02	Case: 13.14 ±1.46 Control: 13.36 ±1.67			0.90 (0.82, 0.98) one-year increase	0.92 (0.84, 0.99)	8/9
Zeydan et al.	2020	US	Case control	124 cases, 318 controls		Case: 12.7±1.5 Control:12.6 ±1.3					8/9
Falaschi et al.	2001	Italy	Case control	76 cases, 50 controls	Case: 34.9±0.9, Control: 33.4±1.7	Case: 12.3±0.2, Control: 12.4±0.2					7/9
Jacobs et al.	2021	UK	Case control	1635 cases, 263058 controls		Case: 12.8± 1.66 / Control: 12.97± 1.62			0.94 (0.91,0.97) Delayed menarche		8/9
Oturai et al.	2016	Denmark	Case control	1827 cases, 4685 controls		Case: 13.1 ±1.5 Control: 13.3 ±1.4			0.95 (0.905, 0.997) one-year increase		-
Rejali et al.	2016	Iran	Case control	200 cases, 200 controls	Case: 31.76 ± 8.13 Control: 31.53 ± 8.97	Case: 12.96± 1.43 Control: 13.48± 1.49	26 ± 7.77	90 % RRMS	0.780 (0.676-0.899) Delayed menarche		7/9
Smith et al.	2016	US	Case control	407 cases, 412 controls					0.49, 95(0.25,0.84) Increase menarche age		-
Ramagopalan et al.	2009	Canada	Case control	4472 cases, 658 controls		Case: 12.4 ±1.29 Control: 12.6 ±1.33			0.90 (0.84,0.95) one-year increase		8/9
Gustavsen et al.	2014	Norway	Case control	391 cases, 918 controls		Case: 13.07 ±1.38 Control: 12.97± 1.43					7/9

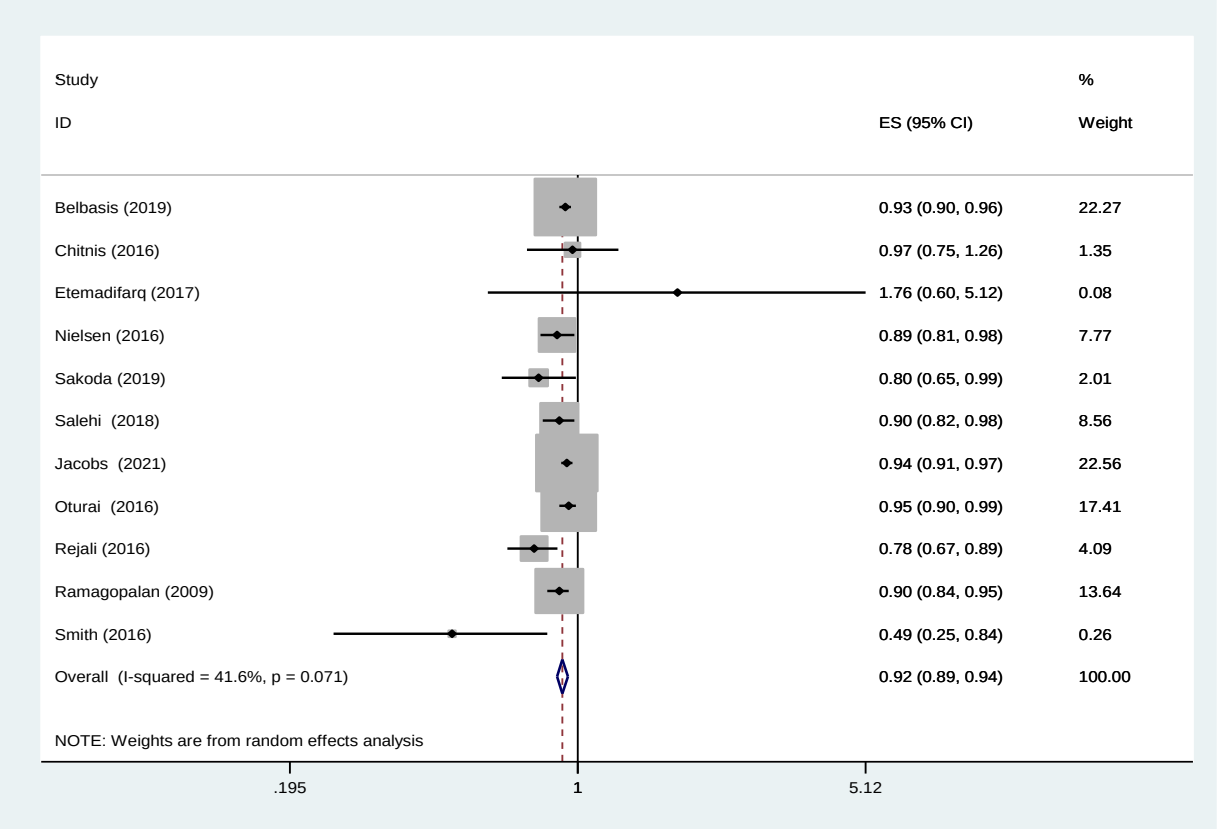

Figure 3: The pooled OR for increasing 1 year of age at menarche

In current study we found that the pooled OR for increasing 1 year of age at menarche and risk of MS is estimated as 0.92, which means that one-year increase of age at menarche decreases the odds of MS by 8%. In ten out of eleven studies which were included for OR estimation, the OR was less than 1(and in 9 the confidence interval did not include 1, showing significancy).

In our previous systematic review and meta-analysis which we included only three studies, the pooled OR was estimated as 0.88 (showing one year increase of age at menarche will result in 12% decrease of MS odds) (10).

We also found that the SMD of age at menarche (controls – cases) in included studies ranged between -0.18 and 1.41, and the pooled SMD of age at menarche (controls-cases) was 0.17, which was significant. In twelve out of fourteen studies the SMD of age at menarche was positive and in two were negative. This finding shows that age at menarche in most included studies were higher in controls than cases.

In a study which was conducted by Chitnis et al, the age at menarche in pediatric MS cases was 11.6 in cases and 11.9 in controls which showed no significant difference. The OR for age at menarche and odds of MS in their study was 0.97 (95% CI: 0.75-1.26), showing no association (13).

In a case-control study in Norway which was done by Gustavsen et al, age at menarche in MS cases was 13.07 and 12.97 in controls (no significant difference) (14), which was in agreement with Zeydan et al findings (15).

Ramagopalan et al, included 4472 MS cases, and 658 spousal controls. They reported significant difference regarding age at menarche between cases and controls. In their study, the OR was 0.9(95% CI: 0.84-0.95), showing significant reduction of odds by increasing age (16).

In a case-control study, Rejali et al included 200 MS cases and 200 controls, and reported significant difference regarding age at menarche (13.48 in controls and 12.96 in cases). The OR of developing MS by one year increase of menarche age at their study was 0.78(95% CI: 0.67-0.89) which was significant (17).

MS is an autoimmune disease that affects women more than men (F/M near 3) (18).

Sex hormones such as estrogen, progesterone, and

testosterone play great role in developing autoimmune diseases by Strong activation of T-cells, more expression of cytokine genes, and increased level of immunoglobulins (6, 7).

Estrogen leads to maturation and differentiation of B cells which play role in developing MS by antigen presentation, cytokines production, and antibody production (19, 20).

Early menarche may imbalance the sex hormone levels and predispose females to develop MS. On the other hand, a recent systematic review and meta-analysis showed that menopause results in relapse reduction and disability improvement in women with MS (21), highlighting the role of sex hormones in autoimmune diseases.

Another systematic review and meta-analysis showed that pregnancy history (compared with nulliparity) decreases the odds of developing MS by 36%(9). Pregnancy may modulate immune system and decrease risk of autoimmune diseases by overall reduction of ro-inflammatory cytokines, and rise in counter-regulatory cytokines (22).

All of these findings show that sex hormones play crucial role in developing and progression of MS.

This systematic review has some strengths. First, the number of included studies is high. Second, we estimated pooled SMD as well as pooled OR.

This study had some limitations. First, all studies did not report mena age at menarche in two groups or ORs.

Second, we did not have studies from all countries to compare the results between continents and countries.

Conclusion

The results of this systematic review show that the mean age at menarche is higher in controls than women with MS, and the risk of MS decreases by increasing age at menarche.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

None.

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Citation: Shahraki Z, Rastkar M, Rastkar E, Ghajarzadeh M, Mohammadifar M. **Does Age at Menarche Differ Between Patients With Multiple Sclerosis and Healthy Controls?: An Updated Systematic Review and Meta-Analysis.** J Family Reprod Health 2025; 19(1): 1-7.