

Early Menarche as a Protective Factor Against Cardiovascular Events: A Systematic Review and Meta-analysis

ABSTRACT

Background: Women are often neglected in cardiovascular health prevention. Age at menarche (AAM) has been linked to cardiovascular (CVD) disease in women and is potentially identified as one of the significant CVD risk factor. However, there is still limited comprehensive evidence addressing this issue. This systematic review and meta-analysis aimed to investigate how early menarche affects the outcome of all-cause mortality, CVD mortality, total cardiovascular disease event, stroke (ischemic, hemorrhagic, and total stroke), and coronary heart disease (CHD).

Method: The Cochrane Library, MEDLINE, Embase, ScienceDirect, and Google Scholar databases were searched from March 2013 to March 2023 for cohorts investigating the effect of early onset of menarche on CVD events with a minimum follow-up period of 5 years. Studies that observed specific population and/or included women with a history of CVD at baseline were excluded. The Newcastle–Ottawa scale was used for risk of bias assessment for each cohort included. The data were presented as dichotomous measure using risk ratios. I^2 statistics were utilized to evaluate the heterogeneity of presented data.

Results: Thirteen cohorts included 18 626 799 female patients with ages ranging from 43 to 62.6 years. These reported 6 estimates each for CHD (5 483 298 patients) and all-cause mortality (1595 878 patients), 5 estimates each for total stroke (2 941 321 patients) and CVD mortality (1 706 742 patients), 4 estimates each for total CVD events (3 988 311 patients) and ischemic stroke (2 434 580 patients), and 1 estimate for hemorrhagic stroke (66 104 patients). Our study found that events of CHD were significantly lower in early menarche (RR 0.57; 95% CI 0.41–0.78; $P < .00001$), as well as total stroke (RR 0.51; 95% CI 0.35–0.73; $P = .0003$), CVD mortality (RR 0.47; 95% CI 0.22–0.98; $P = .04$), total CVD events (RR 0.44; 95% CI 0.25–0.76; $P = .003$), ischemic stroke (RR 0.31; 95% CI 0.15–0.61; $P < .0008$), and hemorrhagic stroke (RR 0.12; 95% CI 0.07–0.20; $P < .00001$); and insignificantly higher in all-cause mortality (RR 0.90, 95% CI 0.76–1.06, $P = .20$).

Conclusion: In our study, cardiovascular events are lower in women with early menarche; hence, the later age of menarche is a potential risk factor to be considered when assessing CVD risk in a patient. However, our sample characteristics were heterogenous, and we did not consider other female hormonal factors that might potentially contribute to the CVD outcomes observed; thus, further studies are needed to clarify.

Keywords: Cardiac function, cardiovascular disease, cardiovascular events

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide.¹ Data showed that total CVD events in adults have increased to around 127.9 million in 2020 with 19.05 million deaths, which amounted to an increase of 18.71% from 2010.² Cardiovascular disease has been estimated to cause around 7 million premature CVD deaths in 2025.^{3,4} Recognition of CVD predisposing factors should be done as early as possible, since they may arise from early in life.

Puberty is a metabolic and physiologic developmental period resulting in the appearance of secondary sexual characteristics and reproductive capacity.^{5,6} Menarche is defined as the first menstrual period in a female adolescent, marking the onset of reproduction. Genetic and environmental factors influence the age

META-ANALYSIS

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at menarche (AAM), with the average age being 12.4 years.^{7,8} Early menarche is defined as menarche before 12 years of age,⁹ while late menarche occurs above 15 years of age.¹⁰ Age at menarche has been identified to be linked with several adult diseases and is associated with obesity, metabolic syndrome, hypertension, and type 2 diabetes, which subsequently increases the risk of CVD.^{8,11,12} However, previous studies have shown conflicting results between early menarche and all-cause mortality or cardiovascular mortality.^{13,14}

This systematic review and meta-analysis aimed to investigate how early menarche affects the outcome of all-cause mortality, CVD mortality, total CVD events, stroke (ischemic and hemorrhagic), and coronary heart disease (CHD).

METHODS

This systematic review and meta-analysis followed the research guideline recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature Search

The literature search was conducted in 5 electronic databases: the Cochrane Library, MEDLINE, Embase, ScienceDirect, and Google Scholar. The key Boolean terms used to identify relevant studies were ("menarche" OR "early menarche" OR "age of menarche") AND ("cardiovascular disease" OR "cardiovascular event"). Additionally, manual screening of the reference lists of all included studies was conducted by two authors independently for additional relevant studies.

Eligibility Criteria

We included cohort studies published in English within the last decade (March 2013–March 2023), which comprised female adults reporting their age of menarche. The studies must have observed endpoints of either CHD, mortality (all-cause and CVD mortality), stroke (hemorrhagic, ischemic, and total stroke), and/or total CVD events (incidence of stroke, CHD, and death in total), with a minimum follow-up period of 5 years. Exclusion criteria were studies that included patients with a history of CV events at baseline and studies that only observed women with a specific disease (e.g., patients with diabetes mellitus, hypertension, metabolic syndrome, cancer, etc.) to avoid analysis bias.

Data Extraction

Two authors independently assessed which studies met the inclusion and exclusion criteria. Any disagreements were

discussed until a consensus was reached. The data extracted from the selected studies included: first author, year of publication, study location, recruitment method, number of participants, gender, mean age, follow-up period, endpoints observed, and the covariates adjusted. Participants with the age at menarche of 12 years or younger were classified into the early menarche group, while participants with the age at menarche of 13 years or older were classified into the control group.

Statistical Analysis

The number of events and total participants from the early menarche and control groups were extracted, choosing the most adjusted model from each cohort. The data analysis was performed using The Cochrane Statistical Package Review Manager version 5.4 (Cochrane Collaboration, London, UK), presented as dichotomous measures using risk ratio (RR) with Mantel–Haenszel random effects model, with a CI of 95%. A two-tailed value of $P < .05$ was considered to be statistically significant. To ascertain the heterogeneity of the presented data, we used the I^2 statistic, with $I^2 < 25\%$ considered to have low heterogeneity, $25\% < I^2 < 75\%$ as intermediate, and $I^2 > 75\%$ as high. For each endpoint assessed, if the number of studies included was 10 or more, a further assessment of publication bias was done through qualitative inspection of the funnel plots.

RESULTS

Search Result

A total of 20852 studies were identified from the initial literature search, and 1042 duplicate studies were excluded. Subsequently, 19765 studies were excluded manually. After screening the abstracts, 19 studies were excluded for not fulfilling the inclusion criteria and 7 due to duplication. The remaining 19 studies were retrieved for their full-length papers and assessed for eligibility. Another 6 studies were later excluded because they did not meet the inclusion criteria ($n = 4$), for other reasons ($n = 1$), or for incomplete data ($n = 1$). A total of 13 met our inclusion criteria and were included in the meta-analysis. The search strategy is presented in Figure 1.

Study Characteristics

Patient characteristics of the included studies are shown in Table 1. All subjects were women. Among the 13 eligible cohorts, the studies took place in a variety of countries including China,^{15,19,24} Japan,¹⁶ United States,^{17,25} UK,^{18,27} Korea,^{20,23,26} Mexico,²¹ and Norway.²² The sample sizes ranged from 647²⁵ to 1224547²³ women. The average age of participants ranged from 43²¹ to 62.6¹⁹ years, and the median follow-up duration ranged from 5.8²⁵ to 18.8¹⁶ years.

Seven endpoints were observed in the 13 cohorts included in this systematic review and meta-analysis, which include: coronary heart disease,^{15–18,20,22,23,26,27} hemorrhagic stroke,²⁰ ischemic stroke,^{16,20,23,26} total stroke,^{15–18,20,22} CVD mortality,^{15,18,19} total CVD events,^{16,17,20,23,25–27} and all-cause mortality.^{19,21,22,25,27}

Risk of Bias in Included Studies

Two authors independently assessed the risk of bias in each included study using the Newcastle–Ottawa Quality

HIGHLIGHTS

- There were consistent data showing lower incidence of major cardiovascular events in women with early onset menarche.
- The risk was significantly lower for coronary heart disease, ischemic stroke, hemorrhagic stroke, total stroke, cardiovascular mortality, and total cardiovascular events in early menarche population.
- The risk for all-cause mortality was also lower, but insignificant.

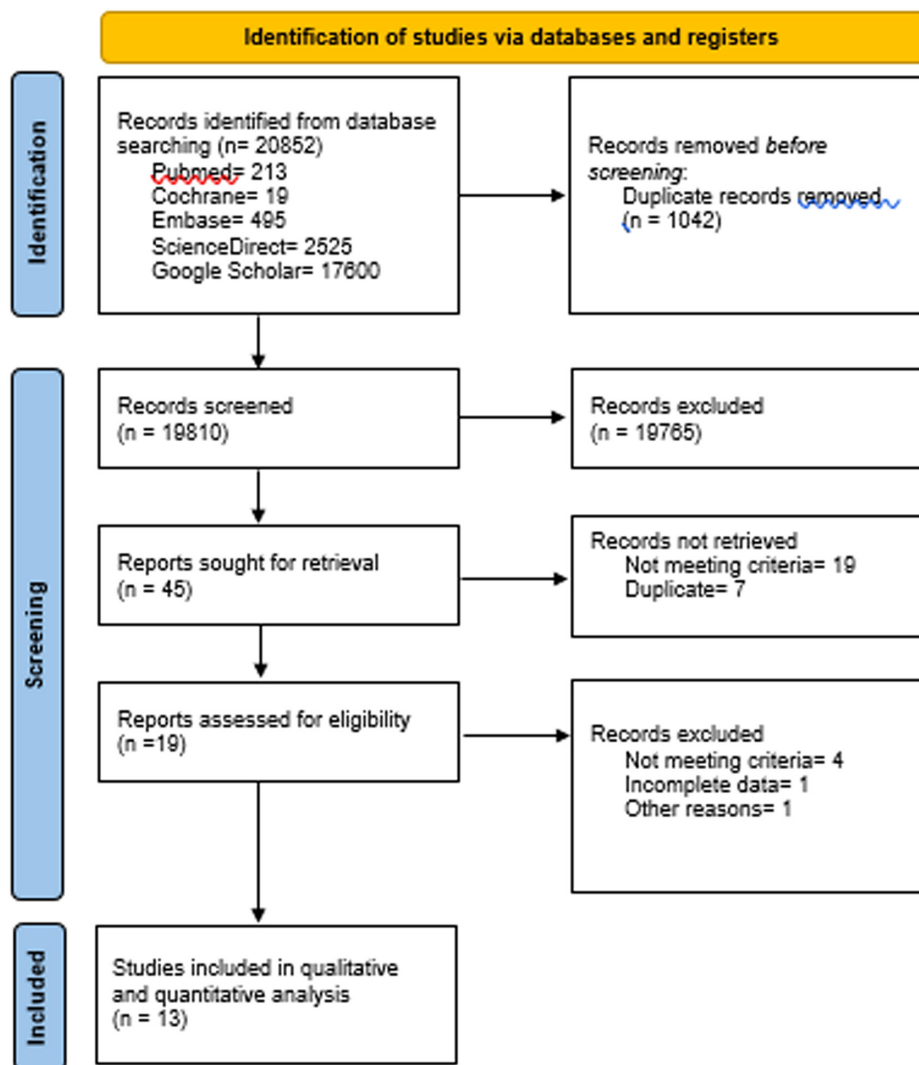


Figure 1. PRISMA flowchart.

Assessment Form for Cohort Studies. Disagreements were resolved by discussion with a third reviewer and by consensus. The risk of bias was assessed by separate criteria, which included selection, comparability, and outcome. Out of 13 studies assessed, 12 (92.31%) studies were of good quality, while 1 (7.69%) study was of fair quality (Table 2).

ENDPOINTS OBSERVED

Coronary Heart Disease

Six cohorts consisting of 5 483 298 patients reported cases of coronary heart disease in 123 750 patients.^{15,17,18,20,23,26} Within 1340 765 patients who had early menarche, coronary heart disease occurred in 30 971 (2.1%) patients, meanwhile 92 779 (2.2%) patients with CHD were found in the control group. Coronary heart disease was significantly lower in early menarche (RR 0.57; 95% CI 0.41-0.78; $P < .00001$); although significant heterogeneity was also found with $I^2 = 99\%$ and $P < .0004$ (Figure 2, Supplementary Figure 1) (Table 3).

Hemorrhagic Stroke

Only one study observed the outcome of hemorrhagic stroke, where it was found to occur in 15 (0.11%) among 14 022

patients in the early menarche group and 475 (0.91%) among 52 082 patients in the control group.²⁰ Hemorrhagic stroke was significantly lower in early menarche (RR 0.12; 95% CI 0.07-0.20; $P < .00001$) (Figure 3, Supplementary Figure 2) (Table 3).

Ischemic Stroke

Four cohorts, which included a total of 2 434 580 patients, reported the occurrence of ischemic stroke.^{16,20,23,26} Ischemic stroke occurred in a total of 519 (0.5%) among 92 026 patients within the early menarche group and 45 874 (1.95%) among 2 342 554 patients within the control and late menarche group. Ischemic stroke was significantly lower in early menarche (RR 0.31; 95% CI 0.15-0.61; $P < .0008$). However, there was significant heterogeneity with $I^2 = 98\%$ and $P < .00001$ (Figure 4, Supplementary Figure 3) (Table 3).

Total Stroke

Total stroke was reported in 5 cohorts, which included a total of 2 941 321 patients.^{15,17,18,20,24} Within the early menarche group, total stroke occurred in 11 469 (0.90%) patients among a total of 1 267 617 patients. On the other hand, within the

Table 1. Characteristics of Included Studies

Reference	Year	Location	Total Subject (Women)	Average Age (Years)	Median Follow-up Duration (Years)	Recruitment Method	Endpoint
Yang et al ¹⁵	2017	China	281 491	50.5	7	China Kadoorie Biobank (CKB)	Stroke, CHD and cardiovascular disease (CVD) death by birth cohort (1920s-1970s)
Ota et al ¹⁶	2023	Japan	54 937	51.2	18.8	The Japan Collaborative Cohort (JACC) Study	CVD, CHD, Stroke; Ischemic stroke, Hemorrhagic stroke
Ley et al ¹⁷	2017	United States	73 814	62.8	33	Nurses Health Study (NHS) data	Total CVD
Canoy et al ¹⁸	2014	UK	1217 840	56	11.6	Routine breast cancer screening by the National Health Service (NHS) screening programs	IHD, Cerebrovascular disease, Incident hypertensive disease
Zhang et al ¹⁹	2019	China	75 359	62.6	12.5	Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort	All-cause mortality, CVD mortality
Jung et al ²⁰	2016	South Korea	66 104	47.3	12.4	Patients who had voluntarily undergone private health examinations in 18 centers	ASCVD, total stroke, thrombotic stroke, IHD, AMI
Lozano-Esparza et al ²¹	2021	Mexico	113 450	43.0	9.2	Mexican Teachers' Cohort	All-cause mortality
Lundblad & Jacobsen ²²	2018	Norway	12 409	46.5	18.7	Tromsø study	All-cause mortality
Jeong et al ²³	2023	Korea	1224 547	61.1	8.4	National Health Insurance Services (NHIS) database of Korea	Myocardial infarction (MI) and ischemic stroke
Hu et al ²⁴	2021	China	16 504	61.4	12	Guangzhou Biobank Cohort Study (GBCS)	Fatal stroke
Lee et al ²⁵	2019	United States	647	58.9	5.8 for MACE, 9.2 for all-cause death	Women's Ischemia Syndrome Evaluation (WISE) study	MACE (the first occurrence of all-cause death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization)
Jeong et al ²⁶	2023	South Korea	1088 922	43.8	8.3	National Health Insurance Service (NHIS) health check-up program and National Cancer Screening Program (NCSP)	CVD, MI, ischemic stroke
Merritt et al ²⁷	2015	London, UK	322 972	50.3	12.9 ± 2.3	The European Prospective Investigation into Cancer and Nutrition (EPIC)	All-cause and cause-specific mortality risk

normal and late menarche group, total stroke occurred in 33533 (2.00%) patients among a total of 1673704 patients. Total stroke was significantly lower in early menarche (RR 0.51; 95% CI 0.35-0.73; $P = .0003$). However, there was significant heterogeneity with $I^2 = 99\%$ and $P < .00001$ (Figure 5, Supplementary Figure 4) (Table 3).

CVD Mortality

Cardiovascular disease mortality was found to occur in 5 cohorts, which included a total of 1706742 patients.^{15,16,18,19,27} Cardiovascular disease mortality occurred in a total of 3043 (0.50%) among 612769 patients within the early menarche group and 11507 (1.00%) among 1093955 patients in the control and late menarche group. Cardiovascular disease mortality was significantly lower in early menarche (RR 0.47; 95%

CI 0.22-0.98; $P = .04$). There was a significant heterogeneity with $I^2 = 100\%$ and $P < .00001$ (Figure 6, Supplementary Figure 5) (Table 3).

Total CVD Events

Four cohorts, which included 3988311 patients, reported total CVD events during follow up.^{17,20,23,26} Cardiovascular disease events occurred in a total of 3864 (0.45%) among 864414 patients within the early menarche group and 76853 (2.46%) among 3123897 patients within the normal and late menarche group. Total CVD events were significantly lower in early menarche (RR 0.44; 95% CI 0.25-0.76; $P = .003$). However, there was significant heterogeneity with $I^2 = 99\%$ and $P < .00001$ (Figure 7, Supplementary Figure 6) (Table 3).

Table 2. Newcastle–Ottawa Scale for Included Cohort Studies

Author	Selection	Comparability	Outcome	Overall	Conclusion
Yang et al ¹⁵	***	*	**	6/9	Good quality
Ota et al ¹⁶	**	*	**	5/9	Fair quality
Lee et al ²⁵	***	*	**	6/9	Good quality
Ley et al ¹⁷	***	*	***	7/9	Good quality
Canoy et al ¹⁸	***	*	***	7/9	Good quality
Zhang et al ¹⁹	***	**	**	7/9	Good quality
Jung et al ²⁰	****	*	***	8/9	Good quality
Lozano-Esparza et al ²¹	***	*	**	6/9	Good quality
Lundblad & Jacobsen ²²	***	*	***	7/9	Good quality
Jeong et al ²³	***	*	***	7/9	Good quality
Hu et al ²⁴	***	*	***	7/9	Good quality
Jeong et al ²⁶	***	*	**	6/9	Good quality
Merritt et al ²⁷	***	*	***	7/9	Good quality

*Represents one score for Newcastle–Ottawa Scale for Cohort Studies.

All-cause Mortality

Based on 6 studies that included a total of 1595 878 patients, there were 8004 (3.47%) cases of all-cause mortality among the 254 004 patients within the early menarche group and 24 912 (1.86%) cases among the 1341874 patients within the control group.^{19,21,22,25-27} All-cause mortality was lower in the early menarche group but insignificant (RR 0.90, 95% CI 0.76-1.06, *P* = .20). There was significant heterogeneity (*I*² = 96%, *P* < .00001) (Figure 8, Supplementary Figure 7) (Table 3).

DISCUSSION

The main findings in this meta-analysis showed that early menarche was a protective factor against MACEs (CHD, ischemic stroke, hemorrhagic stroke, total stroke, cardiovascular mortality, and total cardiovascular events). Jung et al²⁰ demonstrated that this was due to shorter reproductive years. They concluded that early menopause and a shorter duration between menarche and menopause were associated with increased risks of CVD incidence.²⁸ Forman et al³¹ added that early menopause plus short reproductive years (i.e., the interval between the 2 events) were associated with risk for CVD, after adjusting for various risk factors, including smoking status. Late menarche was also known to be associated with low levels of estrogen. Estrogen affects the elasticity of blood vessels and regulates levels of inflammatory markers and lipid, thus having a protective effect on CVD. Estrogen can stimulate nitric oxide synthesis, which plays a role in vasodilation and maintaining CV health.¹¹ Another study

also stated that hypercortisolism and hypoestrogenism are associated with late menarche, as well as low BMI and poor nutrition during puberty. Higher cortisol secretion during puberty can be due to suppression of hypothalamic–pituitary response to gonadotropin hormone-releasing hormone (GnRH), thus inhibiting the action of pulsatile luteinizing hormone (LH). This can result in an increase of atherogenesis.²⁵

Aligned with our findings, the study by Jeong et al²³ found that early menarche was associated with a lower risk of CHD. Two studies^{23,26} also showed that late menarche is associated with CHD events compared to early menarche. In contrast, 2 cohorts^{15,23} found no association between CHD and age of menarche. However, 1 cohort¹⁸ showed that CHD was significantly associated with early menarche, and another¹⁷ showed a non-significant association of CHD with extremely early menarche. The possible explanation for this is that there has been consistent evidence that early menarche is associated with obesity, metabolic syndrome, hypertension, and type 2 diabetes, which subsequently result in an increased risk of atherosclerotic cardiovascular disease (ASCVD). There are at least 2 underlying mechanisms to explain this association, which include endothelial dysfunction and plaque formation, due to the lack of endogenous estrogen as a protective agent in early menarche.^{8,12,18,20,28}

We found that total stroke events were lower in the early menarche population. Similarly, Yang et al¹⁵ found that after excluding women with major CVD risk factors (smoking and

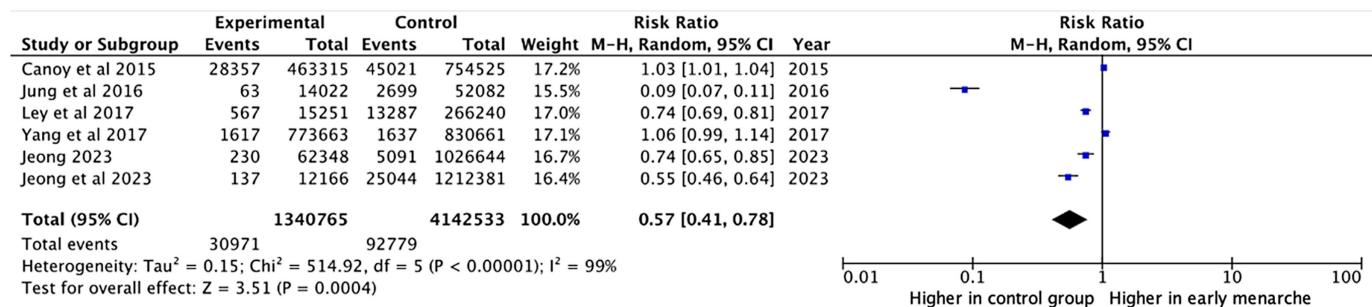


Figure 2. Impact of early menarche on coronary heart disease. [M–H], Mantel–Haenszel method.

Table 3. Summary of the Forest Plot

Endpoint	Number of Studies	Events/Participant			Total Participants	Events		Heterogeneity Between Cohorts		P-value for Differences Across Groups
		Event/EM	Event/CG	Event/CG		Pooled RR	95% CI	P	I ² Statistics	
CHD	6	30 971/13 40 765 (2.30%)	92 779/412 533 (2.24%)	5 483 298	0.57	0.41-0.78	<.0004	99%	<.00001	
Hemorrhagic stroke	1	15/14 022 (0.11%)	475/52 082 (0.91%)	66 104	0.12	0.07-0.20	Not applicable		<.00001	
Ischemic stroke	4	519/92 026 (0.56%)	45874/2 342 554 (1.97%)	2 434 580	0.31	0.15-0.61	<.00001	98%	.0008	
Total stroke	5	11 469/127 617 (0.90%)	33 533/1 673 704 (2.00%)	2 941 321	0.51	0.35-0.73	<.00001	99%	.0003	
CVD mortality	5	30 436/12 769 (0.50%)	11507/1 093 955 (1.00%)	1 706 742	0.47	0.22-0.98	<.00001	100%	.04	
Total CVD events	8	4742/978 714 (0.48%)	81 466/330 167 (2.47%)	4 279 081	0.54	0.38-0.77	<.00001	99%	.0005	
All-cause mortality	6	8004/254 004 (3.15%)	24 903/131 874 (1.86%)	1 595 878	0.9	0.76-1.06	.00001	96%	.2	

CHD, coronary heart disease; CVD, cardiovascular disease.

alcohol drinking), they found that early menarche was still associated with an increased risk of stroke. Our study also showed a significant association between ischemic stroke events and AAM, which is in line with 4^{16,20,23,26} other cohort studies done in the East Asia region (Japan and South Korea). The association between ischemic stroke with AAM was due to the length of estrogen exposure.²³ A short reproductive span and early menopause were found to increase the risk of ischemic stroke with a U-shaped association.²³ Hence, it is crucial to consider these reproductive factors in future studies assessing ischemic stroke and age at menarche. Our study also discovered that hemorrhagic stroke was lower in women with early menarche. This result was aligned with a study conducted by Zhou et al.³² However, the explanation remained unclear.

Two studies^{23,26} showed a lower risk of CVD in women <40 years with early menarche but an increased risk in women >40 years. This could, however, be due to a lower incidence of CVD in the younger population. In contrast to our finding, a study by Ley¹⁷ showed an association between extremely early menarche and a higher risk of CVD, since there was a higher incidence of T2DM and hypertension in samples with extremely early menarche. Although estrogen protects against atherosclerosis, it can increase coagulation by activating intrinsic pathway factors.²³

In our study, we found that CVD mortality was lower in the early menarche population. Two studies^{18,27} found opposing results, although one²⁷ shows that early menarche is associated with an increased risk of CVD mortality. Nevertheless, Yang et al¹⁵ found no association between age at menarche and the risk of CVD mortality. However, in the samples without major CVD risk, a U-shaped association was observed in women who were born after the 1960s. A possible explanation for this phenomenon might be due to the industrialization of China and the difference in wealth between generations, thus leading to a difference in lifestyle and reproductive factors. This implies that patients' lifestyle should be taken into consideration.

A study by Zhang et al¹⁹ did not find any significant association between AAM and CVD mortality; however, when combined with early menopause, it shows that CVD mortality was lower in the early menarche population. Late menopause was also found to slightly attenuate early menarche for CVD mortality. Hence, this study denotes that other hormonal factors such as the onset of menopause should also be considered. Another study by Ota et al¹⁶ found a U-shaped association between age at menarche and the risk of CVD mortality, although not significant. However, no association was found between AAM and mortality specifically due to CHD. A possible explanation might be the low risk of coronary risk factors and heart disease among Japanese women.

Our study showed that all-cause mortality was lower in the early menarche population but insignificant. All-cause mortality comprises many other causes such as women-specific cancer (breast, endometrium, ovary, cervix, and vagina)^{19,21,22,25-27} and other cancer.²¹ Our findings did not consider other factors, e.g., late menarche group as well as the

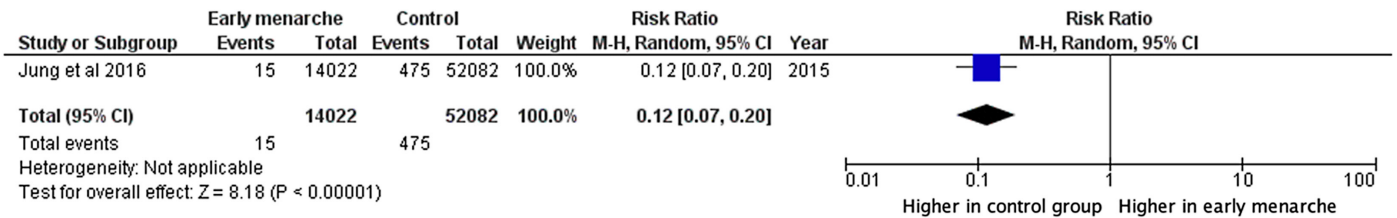


Figure 3. Impact of early menarche on hemorrhagic stroke. [M-H], Mantel-Haenszel method.

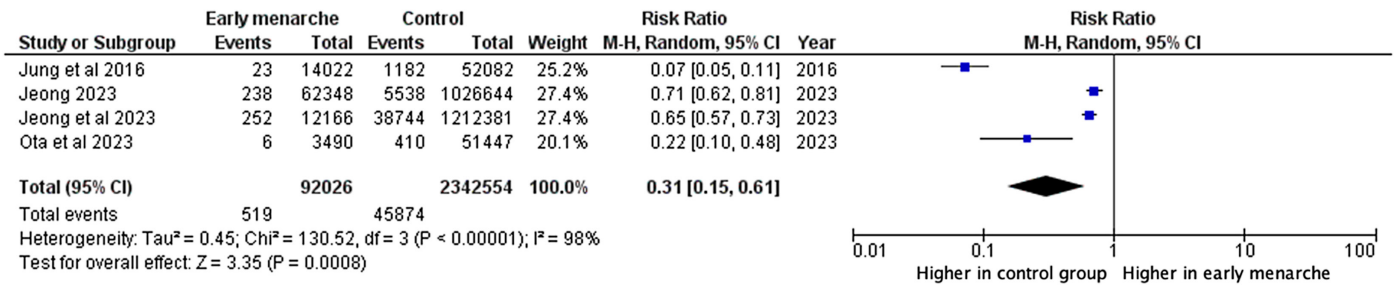


Figure 4. Impact of early menarche on ischemic stroke. [M-H], Mantel-Haenszel method.

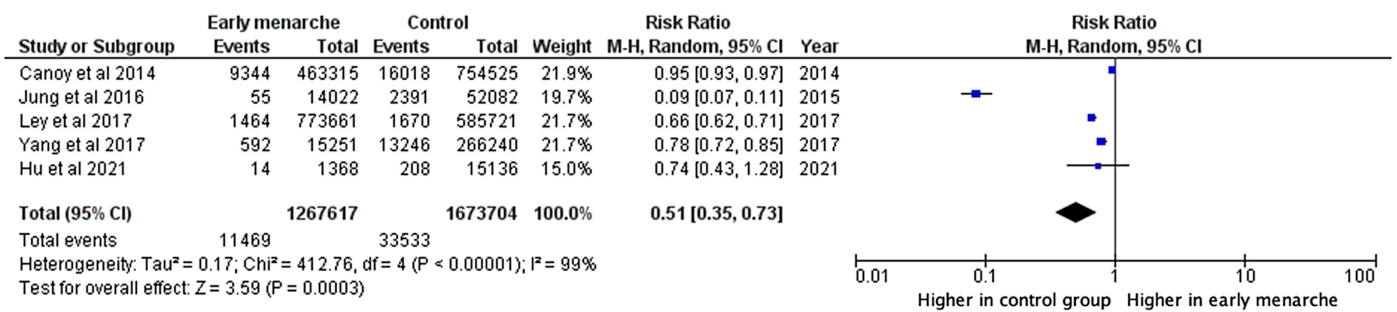


Figure 5. Impact of early menarche on total stroke. [M-H], Mantel-Haenszel method.

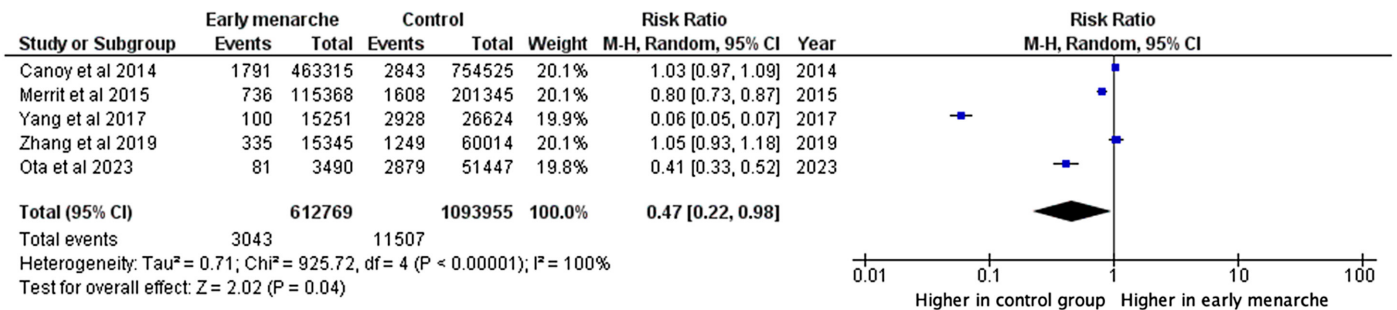


Figure 6. Impact of early menarche on CVD mortality. [M-H], Mantel-Haenszel method.

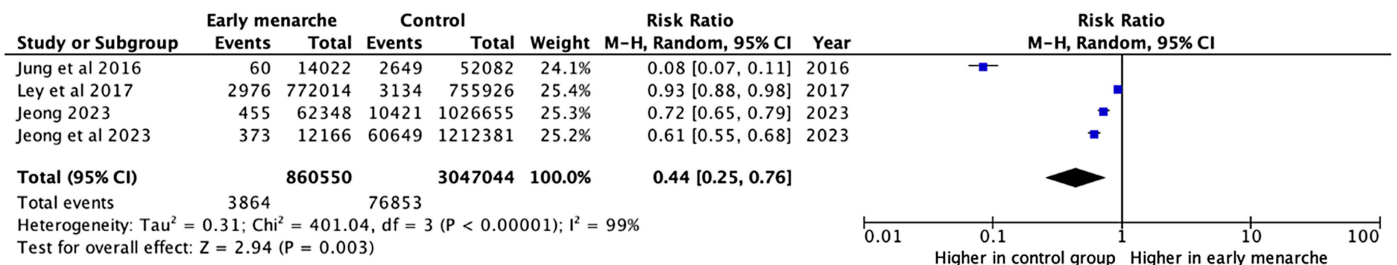


Figure 7. Impact of early menarche on total CVD events. [M-H], Mantel-Haenszel method.

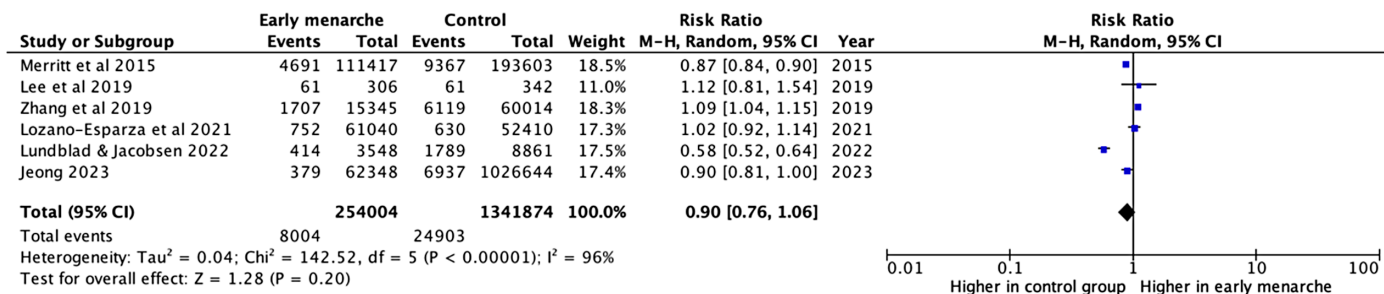


Figure 8. Age of menarche on all-cause mortality. [M-H], Mantel-Haenszel method.

reproductive span, that might have a more significant effect on these outcomes. Reproductive span might be affected by hormonal factors such as the use of hormone replacement therapy, breastfeeding, age at first and last pregnancy, and number of pregnancy.²⁹ There are some potential risk factors for all-cause mortality such as parity, oral contraceptive use, early or late menarche, age at first full-term parity, early menopause, adulthood BMI, and duration of breastfeeding.^{19,21,22,27}

Comparison to Previous Studies

Compared to our review, most of the previous systematic reviews and/or meta-analyses analyzed the relationship of age at menarche with cardiometabolic risk factors other than cardiovascular events (Table 4) Prior studies were primarily focused on analyzing mortality rates rather than the events themselves. Therefore, an updated review is needed to analyze the association of early menarche with both cardiovascular events and cardiovascular deaths. We did a search for systematic reviews adhering to PRISMA guidelines and are aware of only 2 systematic reviews^{14,28} and 1 umbrella review³⁰

published in the last decade that have addressed similar objectives with our study, with the most extensive systematic review²⁸ including 12 cohorts and 2341769 participants. Compared to those reviews, our review analyzed the most outcomes, with a total of 7 outcomes related to cardiovascular events. All of the previous studies included fewer cohorts compared to our study, with 13 cohorts included. However, there are differences in the definition of early menarche used in these reviews. One systematic review²⁸ defines early menarche as menarche before the age of 9.5, while another¹⁴ defines it as menarche before the age of 12. One systematic review³⁰ did not state the definition of early menarche used. Additionally, all of these reviews are relatively outdated, with the most recent review published in 2019. Given that there are new cohorts done between 2019 and 2023, our study offers more updated and comprehensive evidence.

All three previous studies^{14,28,30} did not assess the effects of early menarche on hemorrhagic stroke, ischemic stroke, total stroke, and CHD. Two previous systematic reviews^{28,30} showed consistent results indicating that early menarche

Table 4. Comparison with Previous Studies

Characteristic	Our Study	Chen et al ²⁸	Okoth et al ³⁰	Charalampopoulos et al ¹⁴
Comparison of Study Characteristics				
Type of study	Systematic review and meta analysis	Systematic review and meta analysis	Umbrella review	Systematic review and meta analysis
Year of study	2023	2019	2020	2014
Number of studies included	13 cohort studies	12 cohort studies	32 systematic review and meta analysis studies	9 cohort studies
Early menarche age cutoff	≤12 years	≤9.5 years	No definition	<12 years
Population included	Worldwide	Worldwide	Worldwide	Worldwide
Total patients included	18 626 799	2 341 769	6 074 943	495 391
Comparison of Outcomes				
Total endpoints observed	7	2	2	2
CHD	Yes*	–	–	–
Hemorrhagic stroke	No*	–	–	–
Ischemic stroke	Yes*	–	–	–
Total stroke	Yes*	–	–	–
CVD mortality	No*	No*	No*	No
Total CVD events	Yes*	–	Yes	–
All cause mortality	No*	Yes	–	Yes

Yes, significant association; No, no significant association. CHD, coronary heart disease; CVD, cardiovascular disease. *Lower in the early menarche group.

is not associated with CVD mortality, although none was found to be statistically significant. In spite of that, our results show conflicting results with previous studies for total CVD events and all-cause mortality. Okoth et al³⁰ found that there is a significant association between early menarche and total CVD events, which is contradictory to our findings. Additionally, 2 previous meta-analyses done by Chen et al²⁸ and Charalampopoulos et al¹⁴ found that early menarche is significantly associated with all-cause mortality, though our results showed otherwise, that there is no statistically significant association.

Strength, Limitation, and Implication

Our study pooled and analyzed a big number of samples from 13 cohorts, amounting to 18 626 799 patients in total. There were other systemic reviews and meta-analyses with similar aims, but none had comprehensive CVD endpoint analysis yet. Within our samples, we were able to observe 7 CVD outcomes.

The risk of bias assessment using the Newcastle–Ottawa Scale showed that the majority of the studies included in our research were of good quality. However, the primary limitation of our study was related to the heterogeneous characteristics of the samples included. Thus, careful interpretation of the result should be considered.

Our findings have significant implications in clinical settings, suggesting that AAM should be considered when assessing CVD risk in a patient, especially in the outcomes we found statistically significant. However, our study did not consider other female hormonal factors that might potentially contribute to the observed CVD outcomes, e.g., estrogen exposure, the use of hormonal therapies or contraception, onset of menopause, pregnancy, and breastfeeding duration. Hence, further studies are recommended.

In our systematic review and meta-analysis involving 13 cohorts and 18 626 799 female patients, we found that early menarche was a significant protective factor against the following major cardiovascular events: coronary heart disease, ischemic stroke, hemorrhagic stroke, total stroke, CVD mortality, and total cardiovascular events. Further studies are needed to assess other hormonal factors contributing to cardiovascular outcomes in females.

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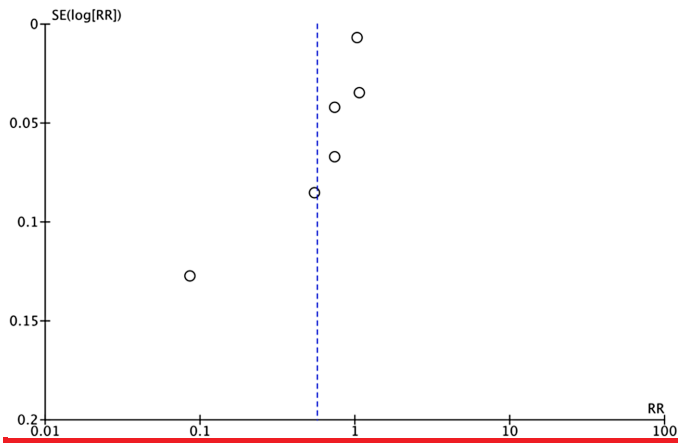
Declaration of Interests: The authors have no conflicts of interest to declare.

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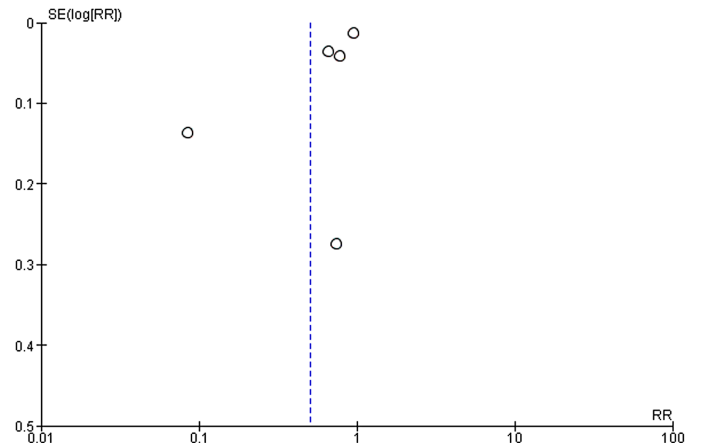
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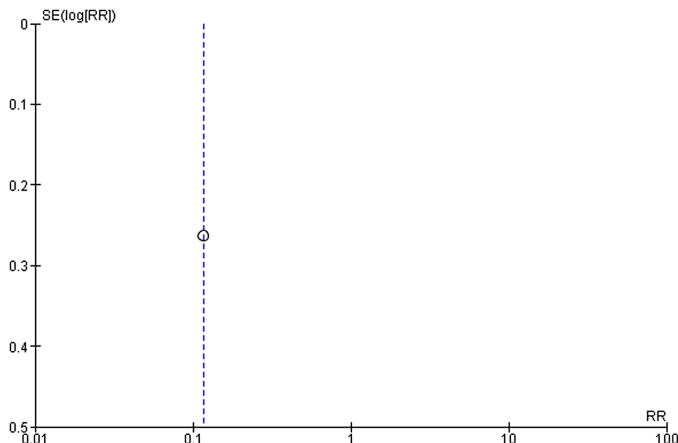
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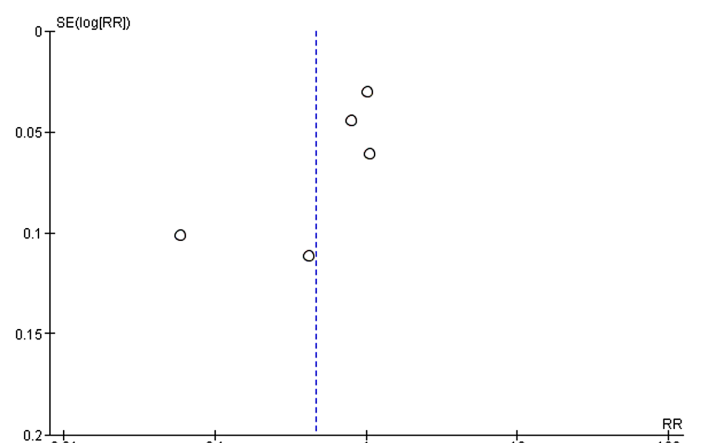
Supplementary Figure 1. Funnel plot representing studies with coronary heart disease as a primary endpoint.



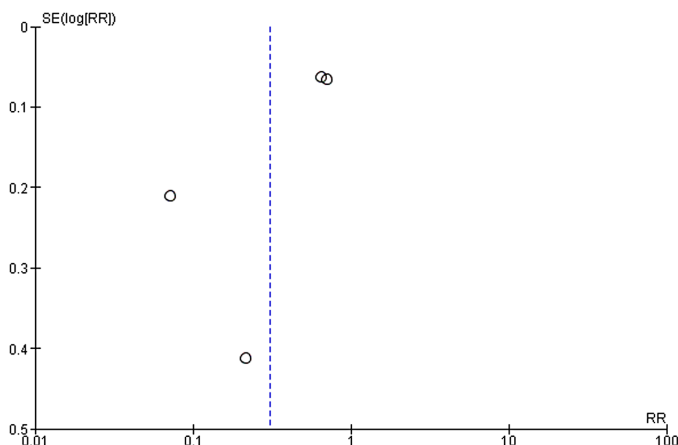
Supplementary Figure 4. Funnel plot representing studies with Total Stroke as a primary endpoint.



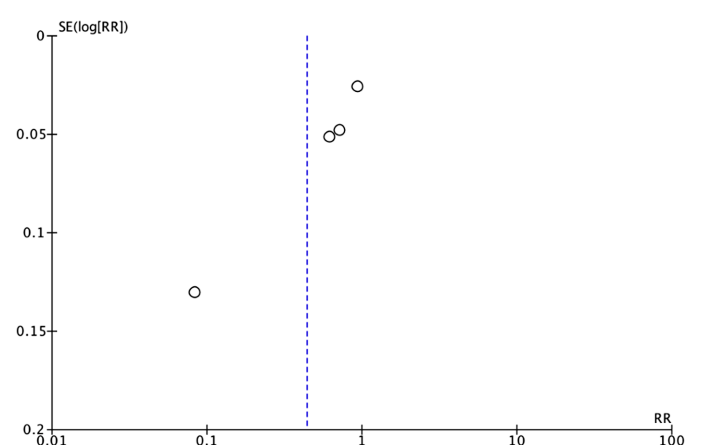
Supplementary Figure 2. Funnel plot representing studies with Hemorrhagic Stroke as a primary endpoint.



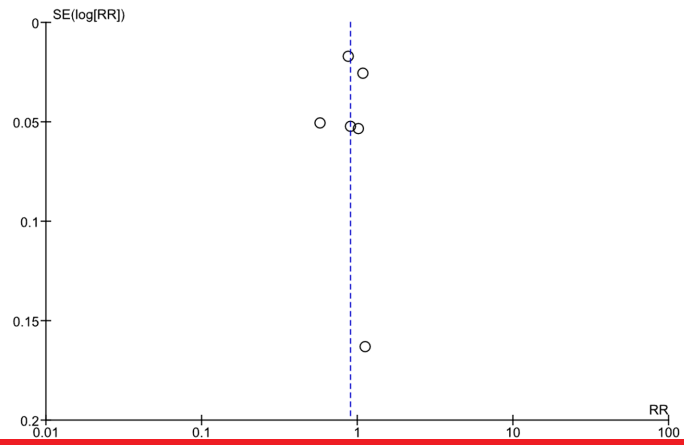
Supplementary Figure 5. Funnel plot representing studies with CVD mortality as a primary endpoint.



Supplementary Figure 3. Funnel plot representing studies with Ischemic Stroke as a primary endpoint.



Supplementary Figure 6. Funnel plot representing studies with CVD events as a primary endpoint.



Supplementary Figure 7. Funnel plot representing studies with all-cause mortality as a primary endpoint.