Risk factors for development of cervical spondylotic myelopathy: results of a systematic review

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ABSTRACT

Study design: Systematic review.

Study rationale: Cervical spondylotic myelopathy (CSM) is a common cause of spinal cord dysfunction that may be asymptomatic or may present with severe symptoms. Since CSM has an insidious manifestation, identification of risk factors associated with this condition may aid clinicians in monitoring high-risk patients and implementing appropriate management strategies.

Objective: To assess sociodemographic, clinical, radiographic, and genetic risk factors associated with presence of CSM in patients 18 years or older.

Methods: A systematic review of the literature was performed using PubMed, the National Guideline Clearinghouse Databases, and bibliographies of key articles to assess risk factors associated with CSM. Articles were reviewed by two independent reviewers based on predetermined inclusion and exclusion criteria. Each article was evaluated using a predefined quality-rating scheme.

Results: From 486 citations, eight articles met all inclusion and exclusion criteria. Larger vertebral body and smaller spinal canal and Torg/Pavlov ratio were associated with CSM diagnosis, while gender was not associated with a CSM diagnosis across multiple studies. There were inconsistent reports with respect to increased age as a risk factor for CSM diagnosis.

Conclusion: The limited data available suggests that inherent anatomical features that may contribute to congenital cervical stenosis may be associated with CSM. This systematic review is limited by the small number of high-quality studies evaluating prognostic factors for CSM. The overall strength of evidence for all risk factors evaluated is low.

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STUDY RATIONALE AND CONTEXT

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction in patients 55 years or older. This disease is caused by the degeneration of various components of the vertebra including the vertebral body, intervertebral disc, supporting ligaments, and the facet and other true joints. These anatomical changes, specifically the development of osteophytic spurs, may lead to the narrowing of the spinal canal and potentially to mechanical compression of the neural elements. Long-standing compression of the spinal cord, in turn, can result in irreversible damage including demyelination and necrosis of the gray matter. The onset of CSM is insidious and usually progresses in a stepwise fashion. Furthermore, CSM may be asymptomatic or may present with a wide range of symptoms, from numb clumsy hands to severe gait impairment [1, 2]. Since CSM has an insidious manifestation, it is essential to determine risk factors associated with this condition. Identification of these factors will allow clinicians to monitor their high-risk patients and implement appropriate management strategies.

OBJECTIVE

To assess sociodemographic, patient, behavioral, environmental, or inborn risk factors associated with the presence of CSM in patients 18 years or older.

MATERIALS AND METHODS

Study design: Systematic review.

Search: PubMed and National Guideline Clearinghouse Databases; bibliographies of key articles (Fig 1).

Dates searched: 1950 through December 2011.

Inclusion criteria: Patients diagnosed with CSM. Studies explicitly designed to evaluate risk factors (sociodemographic, behaviors, occupational or lifestyle, environmental, inborn or inherited characteristics) for CSM in patients older than 18 years were sought. Studies were considered if CSM and evaluation of risk factors were described in the title and/or abstract. Studies which explicitly compared groups which had CSM with those who did not were considered for inclusion. Only studies in which factors logically preceded (or were measured prior to) development of CSM were included.

Exclusion criteria: Cervical radiculopathy diagnosis, cervical spondylosis only with no myelopathy, thoracic and/or lumbar myelopathy, CSM patients with history of acute trauma or tumor, patients younger than 18 years, factors related to recovery after treatment or progress after treatment; factors that related to criteria for CSM diagnosis, clinical assessment, physiological testing; factors that are along the continuum of spondylosis, degenerative spinal disease/processes or its progression; cost-of-care analyses, case series or case reports.

Risk factors: Sociodemographic, patient characteristics, occupational, lifestyle, behavioral, environmental, congenital, inherited and/or genetic factors for CSM.

Outcomes: Cervical spondylotic myelopathy.

Analysis: Descriptive statistics; statistics and effect estimates as reported by authors.

Details about methods can be found in the Web Appendix at www.aospine.org/ebsj
RESULTS

The initial search yielded 486 citations, 21 of which underwent full-text review. Eight studies met the inclusion criteria for assessing prognostic factors associated with CSM diagnosis. One study was a poor quality cohort (Level of Evidence [LoE] III) [3], and seven were considered case-control studies (LoE III) [4–10]. Additional details regarding the critical appraisal and study exclusion criteria are available in the Web Appendix.

Table 1 describes the characteristics of included studies with criteria used for determining the presence (diagnosis) of CSM. Table 2 summarizes the primary factors evaluated in the studies and effect size estimates reported in the studies.

Table 3 sums up findings for factors assessed across multiple studies. Table 4 reviews factors that were evaluated in only one study.

Prognostic factors (Tables 3 and 4)

Sociodemographic, patient, and occupational factors

Only age and gender were evaluated across multiple studies.

- Age: Increased age as a risk factor for CSM was assessed in three studies, two of which found an association between age and diagnosis of CSM.
  - In one case-control study older patients were more likely to have CSM compared with subjects with neck pain but no clinical or radiological evidence of CSM based on multivariate analysis (P = .002) [10].
  - In one retrospective cohort study increased age was an independent risk factors for CSM in a sub-analysis comparing CSM patients with those without CSM (odds ratio = 1.1 per year of age; 95% confidence interval: 1.01–1.14) [3].
  - One study [4] had no statistical relationship between age and CSM diagnosis.

- Gender: Female gender was not associated with the presence of CSM across multiple studies [3, 10].

Findings from single studies:

- Number of working years and working in an extension-strain occupation were not associated with CSM [3].

Inherent or congenital characteristics: characteristics of the spine or spinal canal (based on radiological measurements)

The following measurements were assessed in multiple studies:

- Results across two case-control studies were inconsistent with regard to an association between spinal canal cross-sectional area (CSA) and the presence of CSM [5, 6]. In one study spinal canal CSA was not associated with CSM in a multivariate logistic regression model [5], while in another study smaller spinal canal CSA was associated with CSM in an independent analysis that accounted for sociodemographic and patient factors [6].

- In two case-control studies a larger sagittal diameter of the vertebral body and smaller sagittal diameter of the spinal canal were associated with the presence of CSM [4, 6]. In another study these measurements were associated with CSM in independent analyses that accounted for sociodemographic and patient factors [6].

- In two case-control studies a smaller transverse diameter of the spinal canal was associated with CSM [6, 7]. In one study this spinal canal measurement was associated with CSM in an analysis that accounted for sociodemographic and patient factors [6].

- In two studies a smaller Torg/Pavlov ratio was associated with the presence of CSM [4, 10]. In a case-control study, smaller mean Torg/Pavlov ratios were linked with CSM in a multivariate logistic regression model (P < .0001) [10].

Findings from isolated studies included:

- Smaller CSA of cerebrospinal fluid space [5]; larger vertebral body transverse diameter and CSA, larger sagittal and transverse vertebral body/spinal canal ratios, smaller sagittal and transverse space available for the spinal cord (SAC) [6]; and higher canal-occupying ratio of the spinal cord [7] were associated with CSM in single studies.

- Cross-sectional SAC [6] and dural tube transverse area [7] were not related with CSM in single studies.

Inherited (genetic) factors

- Inherited factors were not evaluated across multiple studies.

- In isolated studies, the following associations with CSM were reported:
  - Having relatives with CSM [8] and vitamin D receptor gene polymorphism [9] were linked with the presence of CSM in single studies.
Table 1  Characteristics of studies reporting prognostic factors for cervical spondylotic myelopathy (CSM).*

| Author                  | Study design      | Demographics                                                                 | Disease/case definition                                                                 | Study population characteristics | F/U, % | CoE   |
|-------------------------|-------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------|--------|-------|
| Poor quality studies (CoE III), controlled for extraneous prognostic factors |                   |                                                                              |                                          |                                  |        |       |
| Golash et al [5] (2001) | Case control      | N=30                                                                          | Symptoms and signs of CSM based on clinical and x-ray findings; myelopathy was assessed clinically based on increased tone, hyperreflexia, decreased power, sensory loss, extensor plantar response | Group 1: CSM (N=20)              | NR III|       |
|                         |                   | Female: 43% Mean age: 39 ± 2.2 (Gr 1) 39 ± 1.5 (Gr 2)                        |                                          | Group 2: Normal controls without symptoms or signs of spondylosis or myelopathy (N=10) |        |       |
| Hukuda et al [6] (1996) | Case control      | N=85                                                                          | Diagnosis of CSM through CT-myelography and satisfying qualification of classic myelopathy; myelopathy was due to cervical spondylosis or OPLL | Group 1: diagnosis of CSM (N=61) | NR III|       |
|                         |                   | Female: 44% Mean age: 56 (range, 22–75; Gr 1) 52 (range, 22–80; Gr 2)       |                                          | Group 2: subjects with spinal lesions other than CSM (N=24)                          |        |       |
| Patel et al [8] (2012)  | Case control      | N=1,486                                                                       | Diagnosis of CSM through registry (ICD-9: 721.1)                                        | Group 1: diagnosis of CSM (N=486) | NR 100%III|       |
|                         |                   | Female: NR Age: NR                                                            |                                          | Group 2: gender-, age- and birthplace-matched controls (N=1000)                      |        |       |
| Takamiya et al [5] (2006)| Retrospective cohort | N=368                                                                        | Diagnosis of cervical myelopathy based on clinical presentation of numbness of bilateral fingers and no other neurological diseases | Group 1: occupation working in cervical extension strain position ≥ 8 h/day, 8 m/o (N=177) | NR III|       |
|                         |                   | Female: 54% Mean age: 51.0 (range, 30–69; Gr 1) 50.8 (range, 30–69; Gr 2)   |                                          | Group 2: did not work in cervical extension strain position (N=191)                  |        |       |
| Wang et al [9] (2010)   | Case control      | N=297                                                                         | Diagnosis of CSM through examination including modified JOA score and MRI imaging; excluded subjects with congenital cervical anomalies, trauma, OPLL, anklyosing spondylitis, cervical inflammatory disease | Group 1: diagnosis of CSM (N=144) | NR III|       |
|                         |                   | Female: 39% Mean age: 45.4 ± 5.5 (Gr 1) 46.1 ± 2.8 (Gr 2)                   |                                          | Group 2: gender- and aged-matched controls with negative MRI findings (N=153)        |        |       |
| Yue et al [10] (2001)   | Case control      | N=116                                                                         | Diagnosis of CSM through x-ray findings (CT-myelography or MRI) and neurological examination; excluded subjects with myelopathy secondary to trauma, OPLL | Group 1: diagnosis of CSM (N=28) | NR 100%III|       |
|                         |                   | Female: 44% Age range: 29–77 (Gr 1) 16–60 (Gr 2)                             |                                          | Group 2: controls with negative neurological examination and x-ray findings (N=88) |        |       |
| Poor quality studies (CoE III), did not control for extraneous prognostic factors |                   |                                                                              |                                          |                                  |        |       |
| Chen et al [4] (1994)   | Case control      | N=200                                                                         | Diagnosis of CSM through neurological symptoms and cervical myelopathy, CT or MRI imaging; had undergone decompressive procedures for cervical myelopathy; excluded myelopathy due to trauma, disc herniation, upper cervical disorders | Group 1: male subjects, diagnosis of CSM (N=100) | NR III|       |
|                         |                   | Female: 0% Mean age: NR                                                       |                                          | Group 2: gender- and aged-matched controls (N=100)                                  |        |       |
|                         |                   |                                                                              |                                          |                                                                                   |        |       |
| Okada et al [7] (1994)  | Case control      | N=170                                                                         | Diagnosis of CSM through neurological examination (JOA score) and radiographic findings | Group 1: diagnosis of CSM (n=74) | NR III|       |
|                         |                   | Female: 42% Mean age: 60.5 (range, 39–84; Gr 1) 46.5 (range, 21–73; Gr 2)   |                                          | Group 2: healthy controls with neck pain and negative neurological examination (n=96) |        |       |

* F/U indicates follow-up; NR, not reported; with regard to percentage follow-up, NR shows that this was not reported or could not be determined as the number of eligible patients and/or number lost to follow-up or without data could not be determined; Gr, group; CT, computed tomography; ICD, International Classification of Diseases; JOA, Japanese Orthopedics Association; MRI, magnetic resonance imaging; OPLL, ossification of posterior longitudinal ligament. Characteristics were reported that related to study question.

† Golash et al [5] (2001): Study population also included a group of subjects with symptoms suggestive of cervical spondylosis, although this group did not meet the inclusion criteria for this systematic review.

‡ Hakuda et al [6] (1996): Classic myelopathy defined as transverse or Brown-Sequard type by Crandall and Batzdorf classification.

§ Hakuda et al [6] (1996): Control population included 4 subjects with metastatic thoracic tumors; 3 thoracic cord tumor; 3 rheumatoid spondylitis; 3 traumatic subluxation of the cervical spine; 2 ossification of the ligamentum flavum of the thoracic spine, thoracic disc herniation; 1 anterior spinal artery syndrome; 1 traumatic thoracic spine dislocation; 1 spinal process fracture of the cervical spine; 1 flexion-extension injury of the cervical spine; 1 cervical spondylotic radiculopathy; and 2 unknown.
### Table 2  Prognostic factors for CSM and outcomes evaluated.*

| Study                                      | Potential prognostic factors evaluated                                      | Significant results†                                                                 |
|--------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| **Poor quality studies (CoE III), controlled for extraneous prognostic factors** |
| **Golash et al [5]** (2001)                | CSA of spinal canal                                                      | Associations with CSM diagnosis (compared with controls):                           |
|                                            | CSA of CSF space                                                         | Smaller CSA of CSF space ($P < .02$)                                               |
| **Hukuda et al [6]** (1996)                | Transverse diameter of vertebral body                                    | Associations with CSM diagnosis (compared with controls):                           |
|                                            | Sagittal diameter of vertebral body                                      | – Larger vertebral body transverse diameter (except C4; $P < .03$ to $P < .0001$)   |
|                                            | CSA of vertebral body                                                    | – Larger vertebral body sagittal diameter (all levels; $P = .03$ to $P < .0001$)   |
|                                            | Transverse diameter of spinal canal                                      | – Larger vertebral body CSA (except C7; $P < .02$ to $P < .0001$)                  |
|                                            | Sagittal diameter of spinal canal                                        | – Smaller spinal canal transverse diameter (all levels; $P < .002$ to $P < .0001$) |
|                                            | CSA of spinal canal                                                       | – Smaller spinal canal sagittal diameter (all levels; $P < .0001$)                 |
|                                            | Ratio between vertebral body and spinal canal (sagittal diameter)        | – Larger ratio between vertebral body and spinal canal (sagittal; all levels; $P < .0001$) |
|                                            | Ratio between vertebral body and spinal canal (transverse diameter)      | – Larger ratio between vertebral body and spinal canal (transverse; all levels; $P < .0007$ to $P < .0001$) |
|                                            | Sagittal SAC                                                             | – Smaller sagittal SAC (except C3, C4; $P < .04$ to $P < .0001$)                   |
|                                            | Transverse SAC                                                           | – Smaller transverse SAC (except C6, C7; $P < .03$ to $P = .002$)                   |
|                                            | Cross-sectional SAC                                                      |                                                                                     |
| **Patel et al [8]** (2012)                  | Familial relationship                                                    | Associations with CSM diagnosis (compared with those without myelopathy):           |
|                                            |                                                                           | – Increased age (OR: $1.1$; 95% CI: $1.01$–$1.14$)                                  |
| **Takamiya et al [3]** (2006)               | Age                                                                       | Associations with CSM diagnosis (compared with controls):                           |
|                                            | Gender                                                                    | – Increased age (OR: $1.1$; 95% CI: $1.01$–$1.14$)                                  |
|                                            | Working years                                                            | – First-degree relative with CSM (RR: $5.21$; 95% CI: $2.07$–$13.1$)               |
|                                            | Extension strain occupation                                               | – Third-degree relative with CSM (RR: $1.95$; 95% CI: $1.04$–$3.7$)                 |
| **Wang et al [9]** (2010)                   | Vitamin D receptor gene polymorphisms                                     | Associations with CSM diagnosis (compared with controls):                           |
|                                            |                                                                           | – ApaI genotype (OR: $2.88$; 95% CI: $1.15$–$4.89$)                                |
|                                            |                                                                           | – TaqI genotype (OR: $4.67$; 95% CI: $2.33$–$5.76$)                                |
| **Yue et al [10]** (2001)                   | Age                                                                       | Associations with CSM diagnosis (compared with controls):                           |
|                                            | Gender                                                                    | – Increased age (OR: $P = .002$)                                                   |
|                                            | Torg/Pavlov ratio†                                                        |                                                                                     |
| **Poor quality studies (CoE III), did not control for extraneous prognostic factors** |
| **Chen et al [4]** (1994)                   | Age                                                                       | Associations with CSM diagnosis (compared with controls):                           |
|                                            | Sagittal diameters of cervical spinal canals                            | – Smaller sagittal diameter of cervical spinal canal ($P < .01$)                   |
|                                            | Sagittal diameters of cervical vertebrae                                | – Greater sagittal diameter of cervical vertebrae ($P < .005$)                    |
|                                            | Torg/Pavlov ratio† from C3-C6                                            | – Smaller Torg/Pavlov ratio ($P < .001$)                                           |
| **Okada et al [7]** (1994)                  | Transverse area of dural tube                                           | Associations with CSM diagnosis (compared with controls):                           |
|                                            | Transverse area of spinal canal                                          | – Smaller spinal canal area at C3 ($P < .001$)                                     |
|                                            | Canal-occupying ratio of the spinal cord†                                 | – Higher canal-occupying ratio of the spinal cord at C3 ($P < .001$)               |

* CSM indicates cervical spondylotic myelopathy; CSA, cross-sectional area; CSF, cerebrospinal fluid; SAC, space available for spinal cord; RR, relative risk; OR, odds ratio; and CI, confidence interval.
† $P < .05$ and effect size estimates as reported by authors.
‡ Torg/Pavlov ratio was obtained by dividing the sagittal diameter of the cervical canal with the sagittal diameter of the cervical vertebra at the same level.
§ Canal-occupying ratio of the spinal cord was not defined; unclear how it was measured.
### Table 3  Summary of sociodemographic factors and characteristics of the spinal cord, canal and vertebral body evaluated as risk factors for CSM reported in two or more studies.*

| Sociodemographic | LoE III, controlled for extraneous prognostic variables | LoE III, did not control for extraneous prognostic variables |
|------------------|--------------------------------------------------------|----------------------------------------------------------|
|                  | Summary | Golash [5] † | Hukuda [6] ‡ | Takamiya [3] † | Yue [10] † | Chen [4] ‡ | Okada [7] ‡ |
| Increased age    | Inconclusive | ↑ | ↑ | NS |
| Female gender    | NS | NS | NS |

**Cord, canal, vertebral body characteristics**

|                      | LoE III, controlled for extraneous prognostic variables | LoE III, did not control for extraneous prognostic variables |
|----------------------|--------------------------------------------------------|----------------------------------------------------------|
|                      | Summary | Golash [5] † | Hukuda [6] ‡ | Takamiya [3] † | Yue [10] † | Chen [4] ‡ | Okada [7] ‡ |
| Smaller spinal canal CSA | Inconclusive | ↑ | ↑ | ↑ |
| Larger vertebral body- sagittal diameter | ↑ | ↑ | ↑ |
| Smaller spinal canal- transverse diameter | ↑ | ↑ | ↑ |
| Smaller spinal canal- sagittal diameter | ↑ | ↑ | ↑ |
| Smaller Torg/Pavlov ratio | ↑ | ↑ | ↑ |

* CSM indicates cervical spondylotic myelopathy; NS, not significant; upward arrow, increased risk for diagnosis of CSM; and CSA, cross-sectional area.
† Controlled for extraneous prognostic factors in multivariate regression analysis.
‡ Assessed gender, body height, body weight, and age on each variable, although no statistics were presented to verify controlling for prognostic factors and specifics of statistical modeling were not provided.
§ Did not control for extraneous prognostic factors.

### Table 4  Summary of factors evaluated as risk factors for CSM in isolated studies.*

|                      | LoE III, controlled for extraneous prognostic variables | LoE III, did not control for extraneous prognostic variables |
|----------------------|--------------------------------------------------------|----------------------------------------------------------|
|                      | Summary | Golash [5] † | Hukuda [6] ‡ | Patel [8] † | Takamiya [3] † | Wang [9] † | Okada [7] ‡ |
| Greater working years | NS |
| Extension strain occupation | NS |

**Cord, canal, vertebral body characteristics**

|                      | LoE III, controlled for extraneous prognostic variables | LoE III, did not control for extraneous prognostic variables |
|----------------------|--------------------------------------------------------|----------------------------------------------------------|
|                      | Summary | Golash [5] † | Hukuda [6] ‡ | Patel [8] † | Takamiya [3] † | Wang [9] † | Okada [7] ‡ |
| Smaller CSA space CSA | ↑ | ↑ | ↑ | ↑ |
| Larger vertebral body-transverse diameter | ↑ |
| Larger CSA of vertebral body | ↑ |
| Larger vertebral body/spinal canal ratio (sagittal) | ↑ |
| Larger vertebral body/spinal canal ratio (transverse) | ↑ |
| Smaller sagittal SAC | ↑ |
| Smaller transverse SAC | ↑ |
| Cross-sectional SAC | NS | NS |
| Dural tube transverse area | NS |
| Higher canal-occupying ratio of the spinal cord | ↑ |

**Inherited (genetic) factors**

|                      | LoE III, controlled for extraneous prognostic variables | LoE III, did not control for extraneous prognostic variables |
|----------------------|--------------------------------------------------------|----------------------------------------------------------|
|                      | Summary | Golash [5] † | Hukuda [6] ‡ | Patel [8] † | Takamiya [3] † | Wang [9] † | Okada [7] ‡ |
| Relatives with CSM | ↑ |
| Vitamin D receptor gene polymorphism | ↑ |

* CSM indicates cervical spondylotic myelopathy; CSA, cross-sectional area; CSF, cerebrospinal fluid; SAC, space available for spinal cord; NS, not significant; and upward arrow, increased risk for diagnosis of CSM.
† Controlled for extraneous prognostic factors in multivariate regression analysis.
‡ Assessed gender, body height, body weight, and age on each variable, although no statistics were presented to verify controlling for prognostic factors and specifics of statistical modeling were not provided.
§ Did not control for extraneous prognostic factors.
CLINICAL GUIDELINES

- Within the limits of our inclusion and exclusion criteria, no clinical guidelines were found that specifically address prognostic factors for CSM.

EVIDENCE SUMMARY

Table 5  What risk factors are associated with the presence (diagnosis) of cervical spondylotic myelopathy (CSM)?

| Prognostic factors      | Strength of evidence | Conclusions/comments                                                                 |
|-------------------------|----------------------|--------------------------------------------------------------------------------------|
| 1. Age                  | Very low             | Increased age was associated with CSM in 2 studies and found to be not associated with CSM diagnosis in 1 study |
| 2. Female gender        | Very low             | Female gender was not associated with CSM in 2 studies                                  |
| 3. Spinal canal CSA     | Very low             | Smaller cross-sectional area of the spinal canal was associated with CSM in 1 study and was not associated with CSM in 1 study |
| 4. Vertebral body sagittal diameter | Very low             | Larger vertebral body sagittal diameter was associated with CSM in 2 studies           |
| 5. Spinal canal transverse diameter | Very low             | Smaller spinal canal transverse diameter was associated with CSM in 2 studies          |
| 6. Spinal canal sagittal diameter | Very low             | Smaller spinal canal sagittal diameter was associated with CSM in 2 studies            |
| 7. Torg/Pavlov ratio    | Very low             | Smaller Torg/Pavlov ratio was associated with CSM in 2 studies                        |

DISCUSSION

- The major finding from this review was that a congenitally narrow spinal canal is a fundamental risk factor for the development of CSM. Multiple studies showed that various measurements reflecting congenital stenosis, including a larger vertebral body (sagittal diameter), smaller spinal canal (transverse and sagittal diameters), and a smaller Torg/Pavlov (T/P) ratio are associated with an increased risk of CSM. In 2009 Pavlov defined a T/P ratio, the ratio of the sagittal diameter of the spinal canal to the anteroposterior diameter of the vertebral body, of 0.82 as indicative of congenital stenosis.

- Interestingly, a few single studies reported specific genetic factors that may be linked with the presence of CSM. One study reported a relationship between various polymorphisms of the vitamin D receptor gene and CSM, specifically patients who are ApaI “A” and Taq “T” allele carriers have an increased risk [9]. A genetic linkage study found an increased risk of CSM between both near and distant relatives [8].

- The independent influence of age on the development of CSM should be addressed in future studies. Two included studies suggested age was related to CSM, while a third study did not find an association.
The overall strength of evidence for various potential risk factors is very low (Table 5). Conclusions from this systematic review are limited by the lack of high-quality studies evaluating factors for CSM. The presence of CSM was based on varying diagnostic criteria provided by the authors of included articles. Additional limitations include disparate CSM case definitions across studies, which did not provide adequate control for potential confounders, limited assessment of true potential risk factors associated with disease, and study designs that prevented the ability to assess the temporality of potential risk factors. Documentation of subject selection and follow-up was poor in most studies.

There is minimal evidence to suggest specific significant risk factors for CSM, and future research is warranted. In particular, it is important to determine factors that may predispose people to CSM to aid with directing appropriate preventive and management programs. Future research using populations with similar disease/case definitions and methodologically rigorous study designs should be used to evaluate potential risk factors for the development of CSM.

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