# CASE-CONTROL STUDY OF RISK FACTORS FOR SPASMODIC DYSPHONIA: A COMPARISON WITH OTHER VOICE DISORDERS

Running Title: CASE-CONTROL STUDY OF SPASMODIC DYSPHONIA

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**ABSTRACT**

**Objectives:** This epidemiology study examined risk factors uniquely associated with spasmodic dysphonia (SD).

**Study Design:** Case-control.

**Methods:** A questionnaire was administered to 150 patients with SD (with and without coexisting vocal tremor) and 136 patients with other structural, neurological, and functional voice disorders (excluding SD and vocal tremor). Questions included personal and family medical histories, environmental exposures, trauma, illnesses, voice use habits and the Short Form 36.

**Results:** Several factors were uniquely associated with SD ($\alpha$=0.05), including: (1) a personal history of cervical dystonia, sinus and throat illnesses, mumps, rubella, dust exposure and frequent volunteer voice use, (2) a family history of voice disorders, (3) an immediate family history of vocal tremor and meningitis, and (4) an extended family history of head and neck tremor, ocular disease, and meningitis. Vocal tremor coexisted with SD in 29% of cases. Measles and mumps vaccines were protective for SD.

**Conclusions:** SD is likely multi-factorial, associated with several endogenous and exogenous factors. Certain viral exposures, voice use patterns, and familial neurological conditions may contribute to the onset of SD later in life.

**Key Words:** spasmodic dysphonia, epidemiology, risk factors, voice disorders

**Level of Evidence:** 3b



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## INTRODUCTION

Spasmodic dysphonia (SD) is believed to be a focal dystonia of the larynx.[1-3] Symptoms typically begin in the fifth decade of life and remain chronic thereafter.[4] Features of SD are action-induced and task-dependent. [5-8] Adductor, abductor, as well as mixed types of SD, have been identified. Adductor SD involves spasms of the laryngeal adductor muscles, causing the vocal folds to over-close involuntarily during speech, creating a strained-strangled voice quality.[9] Abductor SD produces involuntary opening of the vocal folds during speech, resulting in transient breathy phonatory breaks.[10] Both adductor and abductor variants can adversely affect functional communication, leaving many permanently disabled by the condition. There are approximately 50,000 individuals with SD in the US alone, though the condition may be under-diagnosed.[11] No cure exists for SD, with treatment options limited to BOTOX® chemodenervation, laryngeal nerve avulsion, or more recently, denervation-reinnervation surgical procedures.[12-14] These treatments result in only partial remission of symptoms, and are less effective for the abductor variant. BOTOX® is temporary, necessitating regular travel to specialized voice clinics, and may be inaccessible to individuals living in more remote locations.[15] To facilitate the development of more direct and effective treatments, the pathogenesis of SD must be elucidated.

Epidemiologic research has been established as a first-line approach to identify potential contributors to a particular disease or disorder. A National Institutes of Health-sponsored panel recently identified epidemiology as a top priority in SD research.[16] Epidemiology is the study of the frequency, distribution, and causes of diseases in a population. Conventional epidemiologic research methods may be used to identify factors associated with a particular disease or disorder. A *risk factor* is a variable that is associated with a particular disease or disorder, occurring more frequently in the population with the disorder than in the general population. Although risk factors are correlational, and not necessarily causal, risk factors provide insight into the pathogenesis of the disease or disorder under study. Correlational epidemiologic research—sampling a broad range of potentially contributing variables—may be used as the basis for future studies that directly examine identified risk factors to determine disease pathogenesis. Only a few studies have been undertaken with the purpose of identifying possible risk factors that might

be associated with SD. One small report[17] described the onset of voice symptoms in 29 patients with SD. Results related to etiology were equivocal, with 15 individuals reporting SD onset following upper respiratory infection or head or neck trauma. Shortly thereafter, a study was reported involving interviews of 200 patients diagnosed with SD and a control group of 200 individuals with normal voices.[18] The control group included a combination of patients from other ambulatory care clinics, individuals from the general population, and spouses of the patients with SD. The authors were conservative in their interpretation of medical, voice and social history data. However, they indicated that individuals with SD reported histories of more frequent viral and bacterial illnesses, greater frequency of hospitalizations, surgeries, trauma and injury, and a greater frequency of familial neurological conditions. Twenty percent of the patients with SD reported that their voice symptoms began either during or following an upper respiratory or throat condition. However, the authors did not find any significant associations between illness and SD onset. No associations with voice use patterns or occupations were observed. The authors concluded that SD was non-psychogenic and non-behavioral in origin. Although some patients in this study reported that the onset of SD occurred with stress, the authors did not find any significant association. This study was an important initial step toward clarifying the origin of SD, particularly by establishing the lack of association with potential psychogenic factors. However, the diverse control group and lack of conventional epidemiologic sampling procedures and statistical analyses make it difficult to establish risk factors associated with SD. Indeed, the authors strongly recommended caution during the interpretation of these initial findings. A later investigation examined the frequency of neurological disorder comorbidity in 110 individuals with SD.[1] A database of individuals with primary or secondary dystonia was searched to identify those cases with laryngeal involvement. Case history, fiberoptic laryngoscopy, audio-recording, laryngeal electromyography, and neurological evaluation data were collected. Of the 110 SD cases, 66% also had coexisting primary dystonia and 34% had coexisting secondary dystonia. Of the primary dystonia subgroup, 31% had focal dystonia, 25% had segmental cranial dystonia, 46% with dystonia in all segments, and 23% had generalized dystonia; and, familial dystonia was reported in 23% of cases. For the secondary dystonia subgroup, generalized manifestation

was identified in 62% of cases. Electromyography data indicated regular and irregular vocal tremor in 6% and 23% of cases, respectively. In 19% of cases, SD onset was later followed by the presence of additional dystonia symptoms. The authors stressed that SD is a focal dystonia that often coexists with or presents with a family history of other neurological conditions, and that individuals with SD should receive counseling and appropriate treatment related to dystonia comorbidity. Clearly the sampling method employed in this investigation (i.e., cases taken from a cohort of individuals already diagnosed with some other form of dystonia) limits the interpretation of prevalence data related to familial and comorbid neurological symptoms. However, the study provides additional evidence for the possible association of both endogenous and exogenous factors with SD.

More recently, a fairly large-scale investigation was undertaken involving 168 individuals with SD and a first-degree-relative control group.[19] Individuals in the control group were reported to have similar environmental and geographical histories to the SD group. SD diagnosis was confirmed by a multi-disciplinary team including a physician and speech-language pathologist using criteria previously reported in the literature.[20,21] Detailed case histories including medical and family histories, illnesses, environmental exposures, symptom onset, the Voice Handicap Index and the Short Form (SF) 36 were collected. SD participants were identified during routine BOTOX® injection clinic visits. A greater frequency of writer's cramp (11% versus 2%) and essential tremor (26% versus 4%) was observed for the SD group as compared to the control group. For the SD group, 65% had a history of either mumps or measles. Factors that were present at the time of onset included upper respiratory infection (30% of cases) and major life stress (21% of cases). No other familial or environmental factors were uniquely associated with the SD group. Of note, the SD patients also demonstrated statistically significant improvements in Voice Handicap Index scores and social functioning and mental health subtests of the SF-36 after treatment with BOTOX®. This investigation offers further support particularly for the role of exogenous/environmental exposures as possible causes or triggers for SD. The lack of significant neurological or family history findings might be explained by the selection of first-degree relatives as a control group. It is possible that the shared genetic traits and early environmental exposures may account,


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in part, for the absence of findings related to potentially inherited neurological predispositions that might have existed in both groups. These limitations notwithstanding, this study provides motivation for additional case-control epidemiologic studies to isolate risk factors specific to SD. In the first large case-control study employing conventional epidemiologic methodology, our group investigated potential endogenous and exogenous factors in 150 SD cases and 150 medical controls using a previously-vetted questionnaire,[6,7; 22,23] modified to include variables potentially associated with SD.[24] The questionnaire was employed to acquire detailed personal and family medical histories, including an exhaustive list of neurological conditions and symptoms, as well as illnesses, exposures, traumas, and voice use practices. Conventional epidemiologic methods, including sampling procedures and statistical analyses, were used to identify risk factors uniquely associated with SD, as compared with medical-treatment-seeking case controls. Identified risk factors for SD included 1) a personal history of mumps, blepharospasm, tremor, intense occupational and avocational voice use, and a family history of voice disorders; 2) an immediate family history of meningitis, tremor, tics, cancer and compulsive behaviors; and 3) an extended family history of tremor and cancer. Protective factors included the hepatitis vaccine, with greater a frequency of several immunizations reported by the medical control group as compared to the SD group. The results indicated that a combination of inherited and environmental factors might influence SD etiology. Although this study represented an important step in SD epidemiologic research, it did not account for differences that might exist between risk factors associated with voice disorders in general, and those associated specifically with SD. Therefore it is essential to study risk factors for SD within the context of other voice disorders. To that end, the present investigation was undertaken to identify potential inherited and environmental risk factors uniquely associated with SD as opposed to the general classification of voice disorders.

## MATERIALS AND METHODS

### Participant Identification and Recruitment

One hundred and fifty (150) patients with SD and 136 patients with other structural, neurological, and functional voice disorders (excluding SD and vocal tremor) at The University of Utah Voice


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Disorders Center participated in the study (Internal Review Board approval 00025341). Potential participants with SD were identified and recruited in two ways. First, consecutive patients with SD were approached during routine clinic appointments, including initial evaluations, follow-up visits, and laryngeal BOTOX® injection appointments. Second, patients previously seen at our center received a letter and were subsequently telephoned and invited to participate. Of the 192 patients approached and invited to participate, 150 individuals with SD completed the study. Participants recruited for the voice disorders case-control (VC) group included consecutive patients seen during routine clinical appointments, such as initial evaluations, follow-up visits, and voice therapy appointments. Voice disorder control group diagnoses are included in Table I. Of the 160 patients approached and invited to participate, 136 VC individuals completed the study.

Voice disorder diagnosis was confirmed by a multi-disciplinary team of professionals including a laryngologist and one of four speech-language pathologists. Diagnosis was assigned following a thorough evaluation including a detailed case history, auditory-perceptual evaluation, and videolaryngostroboscopy, employing diagnostic criteria previously established and reported.[25-28] Individuals were excluded from the study if they were symptomatic for moderate or severe hearing loss. Other exclusion criteria included diagnosed cognitive impairments.

**Data Collection**

The survey instrument used in this investigation was a previously-validated questionnaire developed for individuals with voice disorders, with additional modifications specific to SD. [6,7; 22,23] Questions included personal and family medical histories—including a detailed neurological history— as well as a history of environmental exposures, trauma, illnesses, voice use habits and the Short Form (SF) 36. The SF-36 is a psychometrically validated general health questionnaire designed to sample physical, psychological, and emotional health and well-being. The SF-36 has been used to determine the relative burden of diseases among different populations. In this study, the SF-36 was administered to determine if differences in overall health between the SD and VC groups might account for any identified risk factors.


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Trained examiners administered the questionnaire to each participant and were periodically audited to ensure accuracy. The questionnaire required approximately one hour to administer.

**Statistical Analysis**

All data were examined using frequencies, proportions, means and standard deviations. The chi-square test for independence was used to determine statistical significance from cross-tabulation bivariate analyses between the SD and VC groups. Odds ratios (*OR*) were obtained using logistic regression, adjusted for potential confounding factors such as age, sex, and income level. The *OR* is a commonly used measure of the probability of exposure among the cases relative to the probability of exposure among the controls. An OR = 1 indicates the exposure does not have an effect on the probability of the disease. On the other hand, if the OR > 1 the exposure increases the probability of the disease, whereas if the OR < 1 then the exposure decreases the probability of the disease. Ninety-five percent confidence intervals were obtained for the estimated *ORs*. Confidence intervals that do not overlap 1.0 indicate statistical significance at a 0.05 alpha level. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA, 2007).

## RESULTS

**Demographics**

Participants ages ranged from 20.4 to 92.5 years (M = 59.7, SD = 14.6) and did not significantly differ between SD and VC participants ($t$ = 1.60, $P$ = 0.112). Years of education ranged from 8 to 23 (Mean = 15.3, SD = 2.5) and did not significantly differ between SD and VC participants ($t$ = - 0.54, $P$ = 0.592). Demographic data for SD and VC groups are presented in Table I. Participants ages 60 to 69 and white (non-Hispanic) were significantly more likely to be in the SD group.

**Short Form (SF) 36**

Scores from the SF-36 were compared for the SD versus VC groups. Multivariate analysis of variance showed that the combination of the eight SF-36 subscales regressed on group was significant (Wilks' Lamda P < 0.001). The scales were transformed to 0-100 and scored so that higher scores represented better health. The specific subscales significantly associated with group were physical


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functioning (M = 85.3 for SD and 75.1 for Control; F = 11.2, P < 0.001; Norm = 84.2), role limitations due to physical health (M = 77.7 for SD and 53.7 for Control; F = 27.9, P < 0.001; Norm = 80.9), energy/fatigue (M = 58.4 for SD and 51.9 for Control; F = 6.0, P = 0.015; Norm = 60.9), social functioning (M = 86.4 for SD and 75.0 for Control; F = 14.5, P < 0.001; Norm = 83.3), pain levels (M = 78.4 for SD and 68.4 for Control; F = 13.1, P < 0.001; Norm = 75.2), and general health (M = 71.8 for SD and 63.3 for Control; F = 10.4, P = 0.001; Norm = 71.9). Role limitations due to emotional stresses (M = 88.4 for SD and 85.5 for Control; F = 0.77, P = 0.380; Norm = 81.3) and emotional well-being (M = 79.7 for SD and 79.6 for Control; F = 0.0, P = 0.963; Norm = 74.7) were not significantly associated with group.

**Endogenous Risk Factors**

Differences between the SD and VC groups based on select medical history variables are presented in Tables II-IV. Factors were included in each table if differences were observed between the groups based on that variable ($\alpha = 0.10$). Statistically significant *ORs* ($\alpha = 0.05$) are indicated in bold. Sampled endogenous factors consisted of an extensive list of neurological diseases and symptoms—including dystonias and tremor variants—as well as central nervous, metabolic, autoimmune and immune system diseases, respiratory conditions, health or medical conditions, personality traits and psychological conditions. For purpose of this study, questions were classified as pertaining to the individual's personal history (PH), immediate family history (IFH)—including included parents, brothers, sisters and children—and extended family history (EFH), including grandparents, grandchildren, aunts, uncles and cousins.

Significant PH factors unique to the SD group are presented in Table II. A statistically significant difference based on a PH of cervical dystonia, with a greater frequency in the SD group, was observed ($\alpha = 0.05$). A family history of voice disorders was also significantly associated with SD (17% for SD versus 7% for VC, $P<0.001$; $OR = 2.7$, $95\%\ CI = 1.2\text{-}6.1$ after adjusting for age, gender, and race). Twenty-nine percent of the participants in the SD group experienced coexisting vocal tremor, and 16% had head or neck tremor.


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Among the SD group, those with head/neck tremor or voice/vocal tremor were significantly more likely to have cervical dystonia (14.3% vs. 4.0%, Chi-square[1] = 5.18, $P = 0.023$). A marginally insignificant relationship was observed between head/neck tremor or voice/vocal tremor and cancer (22.4% vs. 10.9%, Chi-square[1] = 3.52, $P = 0.061$). There were no other significant relationships involving head/neck tremor or voice/vocal tremor and the previous medical conditions listed in Table II.

Significant IFH factors unique to the SD group are presented in Table III. *OR* analyses indicated significantly greater associations with the SD group versus the VC group if they had an IFH of vocal tremor, meningitis and acid reflux ($\alpha = 0.05$). Significant EFH factors unique to the SD group are presented in Table IV. *OR* analyses indicated significantly greater associations with the SD group versus the VC group if the had an EFH of head or neck tremor, ocular disease and meningitis ($\alpha = 0.05$). Among the SD group, there were no other significant relationships involving head/neck tremor or voice/vocal tremor and the previous medical conditions listed in Tables III and IV.

**Exogenous/Environmental Risk Factors**

Differences between the SD and VC groups based on select health symptoms, illnesses, voice use patterns, traumas and environmental exposures are presented in Tables V and VI. Factors were included in each table if differences were observed between the groups based on that variable ($\alpha = 0.10$). Statistically significant *OR*s ($\alpha = 0.05$) are indicated in bold. Exogenous factors sampled included surgeries, traumas/injuries, chemical exposures, viral infections, vaccinations, alcohol/tobacco/drug use, musculoskeletal tension, and voice use patterns. *OR* analyses indicated that individuals were significantly more likely to be in the SD group versus the VC group if they had a greater frequency of sore throats, rubella, and avocational voice use ($\alpha = 0.05$). A statistically significant difference based on a history of having contracted mumps and having extensive dust exposure, with a greater frequency in the SD group, was also observed ($\alpha = 0.05$). Although a high level of both SD and VC groups indicated having ever been employed in a job that required extensive voice use on a daily basis, those in the SD group had been employed in this type of job more years (84.6% for 10 or more years versus 62.4% for 10 or more years, Chi-square[1] = 14.81, $P < 0.001$).


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Among the SD group, we also considered the relationship between those with head/neck tremor or voice/vocal tremor and the variables in Tables V and VI. Those with head/neck tremor or voice/vocal tremor were significantly more likely to have sinus infection at least once per year (46.9% vs. 26.7%, Chi-square[2] = 6.12, P = 0.047). Individuals with head/neck tremor or voice/vocal tremor were also significantly more likely to have had measles (87.0% vs. 69.5%, Chi-square[1] = 5.08, P = 0.024).

**Protective Factors**

Several factors were observed to have significantly greater frequency in the VC group versus the SD group. *OR* analyses indicated significantly greater associations with the VC group for the following factors: 1) a PH of acid reflux, asthma, cancer, neurological symptoms, mood disorders, colds, past choral singing, head trauma with loss of consciousness, measles vaccine, mumps vaccine, head or neck surgery, and trunk or thorax surgery and 2) an EFH of social anxiety and being overly emotional.

## DISCUSSION

This case-control epidemiologic investigation compared a group of individuals with SD (with and without coexisting vocal tremor) to a group of individuals with other structural, functional or neurological voice disorders. The purpose of the study was to identify endogenous and exogenous risk factors unique to SD. This investigation was the first to examine potential causes of SD within the context of other voice disorders, which is critical to ensure that identified factors are specific to SD and are not merely associated with voice problems in general (i.e., to determine specificity versus commonality). Conventional epidemiologic measures, including odds ratio analyses, were employed to isolate risk factors uniquely associated with SD. Several risk factors related to neurological factors, voice use practices, and viral exposures were identified. Protective factors were also identified. A discussion of each of the salient findings from this investigation is provided below.

**Neurological Risk Factors**

A PH of cervical dystonia, as well as a PH and familial history of tremor was significantly associated with the SD group. Individuals with SD plus coexisting tremor were more likely to have cervical dystonia than those with SD only; however, individuals with SD only were still more likely to


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have cervical dystonia than the VC group. This finding is not surprising given the previously reported comorbidity of SD, vocal tremor, and other neurological conditions in the literature. In our group of patients with SD, 29% had coexisting vocal tremor. This finding is consistent with previous reports that approximately one-third of individuals with SD also experience vocal tremor.[1; 18,19] Essential tremor is a risk factor for other forms of adult-onset dystonia,[29,30] and the frequent coexistence of SD and tremor may reflect a neurological vulnerability or predisposition to the development of movement disorders in this population. The coexistence of cervical dystonia in a subset of individuals in the SD group would support this theory, and is also consistent with earlier research documenting the likelihood of more than one regional or segmental dystonia in patients with SD.[1] A recent investigation of 128 individuals with SD and 146 voice disorder controls offered further evidence for the frequent co-occurrence of SD and tremor.[31] Vocal tremor was present in 26% of cases, and non-vocal tremor in 21% of cases. The authors stressed the need for referral to neurology to evaluate such patients for other potentially comorbid neurological conditions. Furthermore, distinguishing essential voice tremor from SD can be difficult, especially as the amplitude of the tremor becomes sufficient to create phonatory breaks in connected speech. This has led to a clinical classification system which includes SD only, SD "with" voice tremor, and SD "of" essential voice tremor. Therefore, studies involving coexisting SD and tremor should consider the problem of potential overlap among SD and vocal tremor variants. It is possible that the comorbidity of SD and tremor may be overestimated due to diagnostic imprecision and overlapping auditory-perceptual features. Laryngeal electromyography, careful auditory-perceptual evaluation, and BOTOX® treatment response may be valuable tools in differential diagnosis.

Individuals with SD were more likely to report a family history of voice disorders. This potentially may reflect the heritability of voice tremor, as almost one-third of our SD cases had coexisting voice tremor. The family history of voice disorders association is also noteworthy when considering the diagnoses included in the VC group, several of which are believed to have familial or shared environmental contributing factors (e.g., personality and noisy environments in vocal nodules).


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Regardless, findings from this investigation indicate that individuals with SD have a greater frequency of cervical dystonia as well as a family history of tremor, and provide additional support for a genetic-transmission model of SD.

**Viral Exposures**

A PH of upper respiratory infections involving sinus or sore throat symptoms, mumps, rubella, and a family history of meningitis were associated with the SD group with greater frequency than the VC group. Individuals who reported an IFH of meningitis were more likely to be in the SD group, and to have a history EFH of meningitis. Experiencing sore throats more than once per year was associated with the SD, as was the presence of sinus infections one or two times per year. The SD group also reported a greater frequency of mumps and rubella than the VC group, 67% versus 51% and 14% versus 7%, respectively. While individuals in the SD group were more likely to have contracted mumps and rubella, individuals with SD plus coexisting tremor subset were also more likely to have contracted measles (87.0% versus 69.5%). Vaccinations for these diseases were protective against SD. In general, these findings are consistent with SD versus medical control comparisons demonstrating the increased frequency of viral exposures in patients with SD.[24]

Viral exposure has been linked to numerous diseases and conditions, including multiple sclerosis, chronic fatigue syndrome, and cancer. Viruses can affect the central or peripheral nervous systems, or both, and can result in neuropathy. For example, viral-induced unilateral vocal fold paralysis and subsequent synkinesis has been described.[32] Mumps is a viral infection that affects the parotid glands that can cause encephalitis—or brain inflammation—and meningitis. Rubella affects the lymph nodes and joints, and can also cause encephalitis, as well as inflammation of the nerves and testicles. Meningitis creates swelling of the leptomeninges and subarachnoid cerebrospinal fluid, affecting the central nervous system. Although most cases of viral meningitis resolve with minimal observable complications, the


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potential for creating subtle changes in the brain that might predispose an individual to developing a focal laryngeal dystonia, such as SD, later in life is unknown.

Changes in the brain associated with the speech control circuits have been identified in patients with SD. Abnormalities in the white matter in the laryngeal motor control circuit, involving the internal capsule and the cerebellum, as well as additional changes in the thalamus, corticobulbar tract, and the basal ganglia have been identified in patients with SD.[3] Structural and functional abnormalities involving gray matter have been demonstrated in the laryngeal primary sensorimotor cortex, the inferior frontal gyrus, the superior/middle temporal and supramarginal gyri, and the cerebellum. Together, these findings indicate complex changes in the brain involving regions of motor execution, motor preparation, and possibly auditory processing regions that are active during speech production.[33] Simonyan and colleagues[3] have suggested that a slow progressive neurodegenerative or metabolic process might be responsive for or contribute to the pathophysiology of SD. We hypothesize that viral exposures might contribute to the neurodegenerative changes observed in these imaging studies. Viral exposures associated with encephalitis seem to be particularly associated with SD pathogenesis.

**Voice Use Factors**

A history of frequent, occupationally intense voice use was prevalent in both the SD and VC groups (82.7% and 80.2%, respectively). The majority of individuals in the SD and VC groups indicated that they had been employed in a job that required extensive voice use on a daily basis. However, those in the SD group had been employed in this type of job for more years (e.g., 84.6% for 10 or more years versus 62.4% for 10 or more years). This finding is consistent with previous SD versus vocally normal control comparisons. Related to avocational voice use, 59% of individuals in the SD group reported a greater frequency of voice demands during volunteer activities, versus 41% of the VC group. Although a history of intense voice use is prevalent in many voice disorders (e.g. vocal nodules, polyps etc.), this pattern appears to be more prominent in SD. It is possible, however, that the relatively large number of


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patients with muscle tension dysphonia, unilateral vocal fold paralysis, and presbylaryngis within the VC group, whose etiologies are not necessarily tied to vocal overuse, may have contributed to this finding. Yet, this is the second study that has identified intense voice use as a risk factor in SD development.[24]

In this regard, repetitive fine motor movements have been linked to the development of focal dystonias.[34] Instrumentalists may experience musicians' dystonia, a task-specific movement disorder of the affected body locus, such as the hands or oral musculature.[35] Several risk factors for musicians' dystonia have been identified, including a family history of the disease, pain—possibly due to trauma, nerve entrapment or overuse—as well as anxiety, which has been theorized to engrain aberrant motor memory.[36-44] Treatment often includes BOTOX® injections, medications such as Trihexyphenidyl, and therapy to modify ergonomics and movement form related to use of the instrument. Perhaps the increased frequency of occupational and avocational voice use in the SD population might be analogous to musicians' dystonia, whereby the repeated muscular movements involved in the onset and offset of voicing might contribute to a focal dystonia of the larynx. Although it is unlikely that voice use habits alone might account for the development of SD, perhaps voice use demands and practices might influence or localize laryngeal dystonia in individuals who are genetically predisposed, or who have experienced other potentially contributing diseases or exposures.

**Additional Considerations**

The SF-36 was administered to establish general health parameters for the SD and VC groups. Psychometrically-validated general health assessments are particularly useful when attempting to identify risks for a particular disease group as compared with a control group, so that any observed associations simply related to disease severity are not erroneously attributed to risk factors. In this study, if the VC group had higher (better) scores than the SD group, it would be critical to distinguish those factors associated with SD selection and those associated with SD disease severity. Interestingly, in the present study, SF-36 scores were lower (worse) for the VC group on the following subtests: physical functioning, role limitations due to physical health, energy/fatigue, social functioning, pain levels, and general health.


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There are a few possible explanations for this difference. Indeed, perhaps the VC group simply experienced inferior overall health than the SD group. Although other demographic variables such as age, income level, and race were not significantly different between the two groups, differences in overall physical health are possible. It is also possible, however, that the group differences might be explained by the VC group perhaps exaggerating the number or severity of symptoms (i.e., somatizing symptoms) related to physical health. The largest diagnostic category in the VC group was muscle tension dysphonia (36%), and increased symptom-reporting (and somatization) has been observed in this patient population.[45,46] However, it should be noted that the emotional health subtests, including role limitations due to emotional stresses and emotional well-being, were not significantly different between groups. Thus, it is important to emphasize that the risk factors that were more prevalent in the SD group versus the VC group were not merely related to differences in general health.

It is also worth mentioning that several factors were more prevalent in the VC group as compared with the SD group, including: 1) a PH of acid reflux, asthma, cancer, neurological symptoms, mood disorders, colds, past choral singing, head trauma with loss of consciousness, measles vaccine, mumps vaccine, head or neck surgery, and trunk or thorax surgery and 2) an EFH of social anxiety and being overly emotional. The measles and mumps vaccines are likely a protective factor for SD, suggesting that receiving the vaccine diminishes the likelihood of contracting the virus, which has been associated with SD pathogenesis. Other factors, such as those associated with reflux, psychological factors, and other somatic complaints may be associated with certain VC diagnoses as discussed previously. However, from the results it seems that vaccination against measles and mumps affords some protective value by reducing the risk for SD development.

It should also be acknowledged that the present investigation represents an initial step toward understanding SD etiology. Error associated with self-report data is a known issue. Future studies involving SD families, including blinded neurological evaluations and voice assessment measures, will be needed to substantiate or refute those findings observed in this cohort.


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## CONCLUSION

SD is likely multi-factorial. Familial risk factors and environmental exposures have been linked to SD. These findings are consistent with current genetic and brain imaging studies that elucidate the pathogenesis and pathophysiology of SD. Future research—modeling associations among inherited risks and environmental exposures—is required to determine the precise mechanism(s) responsible for SD pathogenesis.


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**TABLE I: Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Selected Diagnostic and Demographic Variables**

| Variable | SD | | Control | | *Chi-square* | OR[†] | 95% CI[†] |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Diagnosis | | | | | | | |
| Adductor spasmodic dysphonia | 145 | 97 | 0 | 0 | --- | --- | --- |
| Abductor spasmodic dysphonia | 2 | 1 | 0 | 0 | --- | --- | --- |
| Mixed spasmodic dysphonia | 3 | 2 | 0 | 0 | --- | --- | --- |
| Muscle tension dysphonia | 0 | 0 | 49 | 36 | --- | --- | --- |
| Presbylaryngis | 0 | 0 | 23 | 17 | --- | --- | --- |
| Unilateral vocal fold paralysis | 0 | 0 | 14 | 10 | --- | --- | --- |
| Paresis | 0 | 0 | 11 | 8 | --- | --- | --- |
| Polyp | 0 | 0 | 8 | 6 | --- | --- | --- |
| Nodules | 0 | 0 | 6 | 4 | --- | --- | --- |
| Laryngitis | 0 | 0 | 4 | 3 | --- | --- | --- |
| Parkinson’s Disease | 0 | 0 | 4 | 3 | --- | --- | --- |
| Papilloma | 0 | 0 | 4 | 3 | --- | --- | --- |
| Bilateral vocal fold paralysis | 0 | 0 | 2 | 1 | --- | --- | --- |
| Laryngeal dysplasia | 0 | 0 | 2 | 1 | --- | --- | --- |
| Sulcus vocalis | 0 | 0 | 2 | 1 | --- | --- | --- |
| Cyst | 0 | 0 | 1 | <1 | --- | --- | --- |
| Laryngeal fracture | 0 | 0 | 1 | <1 | --- | --- | --- |
| Leukoplakia | 0 | 0 | 1 | <1 | --- | --- | --- |
| Multiple systems atrophy | 0 | 0 | 1 | <1 | --- | --- | --- |
| Reinke’s edema | 0 | 0 | 1 | <1 | --- | --- | --- |
| Scar | 0 | 0 | 1 | <1 | --- | --- | --- |
| Wegener’s granulomatosis | 0 | 0 | 1 | <1 | --- | --- | --- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gender | | | | | | | |
| Male | 56 | 37 | 40 | 29 | 2.01, 1 | 1.0 | --- |
| Female | 94 | 63 | 96 | 71 | 0.157 | 0.7 | 0.4-1.1 |
| Age | | | | | | | |
| 23-49 | 28 | 18 | 39 | 29 | | 1.0 | --- |
| 50-59 | 43 | 29 | 34 | 25 | 5.07, 3 | 1.7 | 0.9-3.4 |
| 60-69 | 37 | 25 | 24 | 17 | 0.167 | **2.3** | **1.1-4.8** |
| 70+ | 42 | 28 | 39 | 29 | | 1.4 | 0.7-2.8 |
| Race/Ethnicity | | | | | | | |
| White, non-Hispanic | 149 | 99 | 129 | 95 | 5.27, 1 | 1.0 | --- |
| Other | 1 | 1 | 7 | 5 | 0.022 | **0.1** | **0.01-0.96** |
| Education (years) | | | | | | | |
| 12 | 26 | 17 | 22 | 16 | | 1.0 | --- |
| 13-15 | 50 | 33 | 49 | 36 | 0.391, 3 | 0.8 | 0.4-1.7 |
| 16-17 | 40 | 27 | 33 | 24 | 0.942 | 1.0 | 0.5-2.0 |
| 18+ | 34 | 23 | 32 | 24 | | 0.9 | 0.4-1.9 |
| Gross Annual Income | | | | | | | |
| < $20,000 | 8 | 5 | 12 | 9 | | 1.0 | --- |
| $20,000 - $39,999 | 17 | 11 | 19 | 14 | 6.934, 4 | 1.1 | 0.3-3.4 |
| $40,000 – $59,999 | 21 | 14 | 30 | 22 | 0.1392 | 0.9 | 0.3-2.6 |
| ≥ $60,000 | 76 | 51 | 58 | 43 | | 1.7 | 0.6-4.6 |
| Do not know | 28 | 19 | 17 | 12 | | 2.1 | 0.7-6.3 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.

**TABLE II: Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Personal History Factors**

| Variable | SD | | Control | | *Chi-square* | OR[†] | 95% CI[†] |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Cervical Dystonia | | | | | | | |
| No | 139 | 93 | 133 | 98 | 0.045 | 1.0 | --- |
| Yes | 11 | 7 | 3 | 2 | | 3.4 | 0.9-12.8 |
| Parkinson's Disease | | | | | | | |
| No | 149 | 99 | 131 | 96 | 0.076 | 1.0 | --- |
| Yes | 1 | 1 | 5 | 4 | | 0.2 | 0.0-1.2 |
| Diabetes | | | | | | | |
| No | 140 | 93 | 119 | 88 | 0.092 | 1.0 | --- |
| Yes | 10 | 7 | 17 | 12 | | 0.5 | 0.2-1.2 |
| Hypertension | | | | | | | |
| No | 104 | 69 | 107 | 79 | 0.073 | 1.0 | --- |
| Yes | 46 | 31 | 29 | 21 | | 1.5 | 0.9-2.4 |
| Acid Reflux | | | | | | | |
| No | 94 | 63 | 50 | 37 | < 0.001 | 1.0 | --- |
| Yes | 56 | 37 | 86 | 63 | | **0.3** | 0.2-0.5 |
| Asthma | | | | | | | |
| No | 128 | 85 | 101 | 74 | 0.019 | 1.0 | --- |
| Yes | 22 | 15 | 35 | 26 | | **0.5** | 0.3-0.9 |
| Cancer | | | | | | | |
| No | 128 | 85 | 102 | 75 | 0.028 | 1.0 | --- |
| Yes | 22 | 15 | 34 | 25 | | **0.4** | 0.2-0.8 |
| Neurological Symptoms | | | | | | | |
| No | 138 | 92 | 114 | 84 | 0.033 | 1.0 | --- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yes | 12 | 8 | 22 | 16 | | **0.4** | 0.2-0.8 |
| Mood Disorders | | | | | | | |
| No | 147 | 98 | 126 | 93 | 0.030 | 1.0 | --- |
| Yes | 3 | 2 | 10 | 7 | | **0.2** | 0.1-0.9 |
| Interpersonal Sensitivity | | | | | | | |
| No | 143 | 95 | 122 | 90 | 0.068 | 1.0 | --- |
| Yes | 7 | 5 | 14 | 10 | | 0.4 | 0.2-1.1 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.

**TABLE III: Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Immediate Family History Factors**

| Variable | SD | | Control | | *Chi-square* | OR[†] | 95% CI[†] |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Vocal Tremor | | | | | | | |
| No | 138 | 92 | 133 | 98 | 0.028 | 1.0 | --- |
| Yes | 12 | 8 | 3 | 2 | | **5.1** | 1.2-20.0 |
| Leg/Foot Tremor | | | | | | | |
| No | 150 | 100 | 131 | 96 | 0.018 | --- | --- |
| Yes | 0 | 0 | 5 | 3 | | | |
| Acid Reflux | | | | | | | |
| No | 101 | 67 | 105 | 77 | 0.063 | 1.0 | --- |
| Yes | 49 | 33 | 31 | 23 | | **1.8** | 1.0-3.1 |
| Ocular (eye) disease | | | | | | | |
| No | 115 | 77 | 115 | 85 | 0.093 | 1.0 | --- |
| Yes | 35 | 23 | 21 | 15 | | 1.6 | 0.9-2.9 |
| Meningitis | | | | | | | |
| No | 134 | 89 | 130 | 96 | 0.047 | 1.0 | --- |
| Yes | 16 | 11 | 6 | 4 | | **2.9** | 1.1-8.1 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.

**TABLE IV. Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Extended Family History Factors**

| Variable | SD | | Control | | *Chi-square* | OR† | 95% CI† |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Head/neck tremor | | | | | | | |
| No | 142 | 95 | 135 | 99 | 0.026 | 1.0 | --- |
| Yes | 8 | 5 | 1 | 1 | | **8.2** | 1.0-68.2 |
| Blepharospasm | | | | | | | |
| No | 142 | 95 | 134 | 99 | 0.076 | 1.0 | --- |
| Yes | 8 | 5 | 2 | 1 | | 3.9 | 0.8-20.0 |
| Ocular (eye) disease | | | | | | | |
| No | 138 | 92 | 134 | 99 | 0.011 | 1.0 | --- |
| Yes | 12 | 8 | 2 | 1 | | **6.3** | 1.4-28.9 |
| Meningitis | | | | | | | |
| No | 140 | 93 | 134 | 99 | 0.029 | 1.0 | --- |
| Yes | 10 | 7 | 2 | 1 | | **6.2** | 1.1-35.0 |
| Interpersonal sensitivity | | | | | | | |
| No | 147 | 98 | 128 | 94 | 0.088 | 1.0 | --- |
| Yes | 3 | 2 | 8 | 6 | | 0.3 | 0.1-1.2 |
| Distrust of others | | | | | | | |
| No | 150 | 100 | 133 | 98 | 0.068 | --- | --- |
| Yes | 0 | 0 | 3 | 2 | | --- | --- |
| Social anxiety | | | | | | | |
| No | 147 | 98 | 127 | 93 | 0.052 | 1.0 | --- |
| Yes | 3 | 2 | 9 | 7 | | 0.3 | 0.8-1.2 |
| Overly emotional | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No | 149 | 99 | 128 | 94 | 0.012 | 1.0 | --- |
| Yes | 1 | 1 | 8 | 6 | | **0.1** | 0.0-0.9 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.

**TABLE V. Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Selected Health Symptoms and Voice Use Patterns**

| Variable | SD | | Control | | *Chi-square* | OR[†] | 95% CI[†] |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Colds | | | | | | | |
| < 1 per year | 43 | 29 | 38 | 28 | 0.003 | 1.0 | --- |
| 1-2 per year | 90 | 60 | 62 | 46 | | 1.3 | 0.7-2.2 |
| ≥ 3 per year | 17 | 11 | 36 | 26 | | **0.4** | 0.2-0.9 |
| Sinus | | | | | | | |
| < 1 per year | 100 | 67 | 101 | 74 | 0.028 | 1.0 | --- |
| 1-2 per year | 34 | 23 | 15 | 11 | | **2.3** | 1.2-4.5 |
| ≥ 3 per year | 16 | 11 | 20 | 15 | | 0.7 | 0.4-1.6 |
| Throat | | | | | | | |
| < 1 per year | 19 | 13 | 40 | 29 | 0.001 | 1.0 | --- |
| 1-2 per year | 67 | 45 | 43 | 32 | | **2.9** | 1.4-5.7 |
| ≥ 3 per year | 64 | 43 | 53 | 39 | | **2.1** | 1.0-4.1 |
| Post nasal drip | | | | | | | |
| Chronic | 26 | 17 | 34 | 25 | 0.019 | 1.0 | --- |
| Seasonal | 27 | 18 | 21 | 15 | | 1.8 | 0.8-4.1 |
| Occasional | 54 | 36 | 61 | 45 | | 1.3 | 0.7-2.4 |
| Not at all | 43 | 29 | 20 | 15 | | **2.7** | 1.3-5.7 |
| Choral singing – past | | | | | | | |
| No | 90 | 60 | 58 | 43 | 0.003 | 1.0 | --- |
| Yes | 60 | 40 | 78 | 57 | | **0.4** | 0.3-0.8 |
| Voice use during other volunteer activities –past | | | | | | | |
| No | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yes | 61 | 41 | 80 | 59 | 0.002 | 1.0 | --- |
| | 89 | 59 | 56 | 41 | | **1.8** | 1.1-3.0 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.

**TABLE VI. Frequency Distributions of the Spasmodic Dysphonia and Voice Disorders Control Groups According to Selected Illnesses, Environmental Exposures and Traumas**

| Variable | SD | | Control | | *Chi-square* | OR† | 95% CI† |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | *P* value | | |
| Chemical Exposure | | | | | | | |
| No | 127 | 85 | 107 | 79 | 0.081 | 1.0 | --- |
| Yes | 16 | 10 | 26 | 19 | | 0.5 | 0.3-1.0 |
| Don't know | 7 | 5 | 3 | 2 | | 2.1 | 0.5-8.6 |
| Head Trauma with loss of consciousness | | | | | | | |
| No | 126 | 84 | 101 | 74 | 0.030 | 1.0 | --- |
| Yes | 22 | 15 | 35 | 26 | | **0.5** | 0.3-0.9 |
| Don't know | 2 | 1 | 0 | 0 | | | |
| Chest/trunk trauma | | | | | | | |
| No | 141 | 94 | 120 | 88 | 0.085 | 1.0 | --- |
| Yes | 9 | 6 | 16 | 12 | | 0.4 | 0.2-1.1 |
| Measles | | | | | | | |
| No | 35 | 23 | 42 | 31 | 0.067 | 1.0 | --- |
| Yes | 106 | 71 | 92 | 67 | | 4.3 | 0.5-21.6 |
| Don't know | 9 | 6 | 2 | 1 | | 0.9 | 0.5-1.8 |
| Mumps | | | | | | | |
| No | 45 | 30 | 59 | 43 | 0.022 | 1.0 | --- |
| Yes | 101 | 67 | 70 | 51 | | 1.6 | 0.9-2.7 |
| Don't know | 4 | 3 | 7 | 5 | | 0.8 | 0.2-3.1 |
| Rubella | | | | | | | |
| No | 109 | 73 | 114 | 84 | 0.046 | 1.0 | --- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yes | 21 | 14 | 9 | 7 | | **2.5** | 1.1-5.8 |
| Don't know | 20 | 13 | 12 | 9 | | 1.6 | 0.8-3.6 |
| Vaccine - Measles | | | | | | | |
| No | 67 | 45 | 46 | 34 | 0.005 | 1.0 | --- |
| Yes | 51 | 34 | 72 | 53 | | **0.5** | 0.3-0.8 |
| Don't Know | 32 | 21 | 18 | 13 | | 1.0 | 0.5-2.1 |
| Vaccine - Mumps | | | | | | | |
| No | 78 | 52 | 51 | 37 | 0.003 | 1.0 | --- |
| Yes | 42 | 28 | 65 | 48 | | **0.4** | 0.2-0.7 |
| Don't Know | 30 | 20 | 20 | 15 | | 0.9 | 0.4-1.7 |
| Vaccine - Rubella | | | | | | | |
| No | 60 | 40 | 46 | 34 | 0.017 | 1.0 | --- |
| Yes | 49 | 33 | 66 | 48 | | 0.6 | 0.3-1.1 |
| Don't Know | 41 | 27 | 24 | 18 | | 1.2 | 0.6-2.4 |
| Vaccine – Swine flu | | | | | | | |
| No | 84 | 56 | 98 | 72 | 0.019 | 1.0 | --- |
| Yes | 17 | 11 | 10 | 7 | | 2.1 | 0.9-5.0 |
| Don't Know | 49 | 33 | 28 | 21 | | **2.3** | 1.3-4.1 |
| Dust – Past exposure | | | | | | | |
| No | 36 | 24 | 47 | 35 | 0.049 | 1.0 | --- |
| Yes | 114 | 76 | 89 | 65 | | 1.6 | 0.9-2.7 |
| Fumes from cleaning products – Past exposure | | | | | | | |
| No | 72 | 48 | 79 | 58 | 0.088 | 1.0 | --- |
| Yes | 78 | 52 | 57 | 42 | | 1.5 | 0.9-2.5 |
| Surgery – Head/neck | | | | | | | |
| No | 15 | 77 | 56 | 41 | < 0.001 | 1.0 | --- |
| Yes | 35 | 23 | 80 | 59 | | **0.2** | 0.1-0.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Surgery – Chest/thorax | | | | | | | |
| No | 136 | 91 | 113 | 83 | 0.057 | 1.0 | --- |
| Yes | 14 | 9 | 23 | 17 | | **0.5** | 0.2-0.9 |

Bolded odds ratios statistically significant, $P < 0.05$.
[†]Adjusted for age, gender, and race/ethnicity.