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The prevalence of dysautonomia in chronic musculoskeletal pain: a systematic review and meta-analysis

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Abstract

Objectives: Several chronic musculoskeletal disorders are characterized by pain, fatigue, dizziness and other associated symptoms that may be related to autonomic dysfunction. The aim of this review was to estimate the prevalence of autonomic dysfunction in chronic musculoskeletal pain (CMP) conditions.

Methods: MEDLINE and EMBASE were searched through to 4th October 2024 for all peer-reviewed studies of dysautonomia in adult musculoskeletal conditions. Risk of bias was assessed using an adapted Newcastle Ottawa scale. The prevalence of dysautonomia and relative risk compared to healthy controls were estimated using random effects meta-analysis.

Results: 17 studies (13 fibromyalgia, 3 Ehlers-Danlos syndrome, one rheumatoid arthritis) were identified, including 1003 participants with musculoskeletal pain and 417 healthy controls. In people with chronic musculoskeletal pain, the pooled prevalence of dysautonomia was 64% (95% CI: 51% to 76%; I^2=93%), more than twice as likely as healthy controls (pooled risk ratio 2.28; 95% CI: 1.51 to 3.45; I^2 = 24%). Most studies objectively assessed the neurocardiovascular system.

Conclusion: The high prevalence of dysautonomia in patients with chronic musculoskeletal painful conditions illustrates the association between dysautonomia and chronic pain, suggesting regular screening for dysautonomia is warranted for all patients with chronic musculoskeletal pain.

Lay summary

In the UK, 28 million adults, mostly women, suffer from chronic pain, defined as pain lasting three months or more. Age is a risk factor that increases the prevalence, with many cases linked to problems in muscles, bones, and joints referred to as chronic musculoskeletal pain.

Dysautonomia is a condition where the autonomic nervous system, which controls automatic body functions such as heart rate, digestion, and blood pressure, does not function properly. In this study, we analysed all previous studies on the link between dysautonomia and chronic musculoskeletal pain. We found that about two-thirds of people with chronic musculoskeletal pain also experience symptoms of dysautonomia.

Our impression is that it is important to consider dysautonomia when treating any patient with chronic musculoskeletal pain. This could provide new approaches to reduce chronic pain and improve outcomes.

Keywords

Autonomic dysfunction; orthostatic intolerance; cardiovascular; neuropathic pain; inflammatory; non-inflammatory; arthritis; chronic widespread pain

Key messages

1. Dysautonomia is not well recognised and often overlooked in patients with painful musculoskeletal conditions.
2. Our review suggests 64% of patients with chronic musculoskeletal pain have dysautonomia.
3. Chronic musculoskeletal pain patients need to be screened for dysautonomia using subjective and objective assessments to inform a comprehensive management plan.

Introduction

Chronic musculoskeletal pain (CMP) is defined as continuous or recurring pain that originates directly from bones, joints, muscles, or related soft tissues due to an underlying disease process, and lasting longer than 3 months (Treede et al., 2019). Examples include inflammatory conditions such as rheumatoid arthritis, osteomyelitis and gout, as well as non-inflammatory or structural conditions like osteoarthritis, and disorders of the tendons or muscles (Treede et al., 2015).

CMP has been recognised as an important predictor of functional impairment globally (Rundell et al., 2019; Welsh et al., 2020), requiring assessment and treatment comparable to other chronic conditions (IASP, 2010). Research in CMP has largely focused on pain-related outcomes, overlooking non-pain symptoms that may significantly influence the overall impact of this condition (Lyng et al., 2023). Many of these non-pain features may be linked to the autonomic nervous system (ANS), which regulates a wide range of physiological functions and is increasingly recognized as an important contributor to various health conditions, including pain. The ANS may indirectly impact the musculoskeletal system through its role in pain recognition and emotional state regulation (Chaves et al., 2021). Chronic pain patients have been shown to have a malfunctioning central autonomic network (CAN) and reduced grey matter which are also implicated in dysautonomia (Yeater et al., 2021)

Autonomic dysfunction, also known as dysautonomia, is an umbrella term that signifies a disturbance of the ANS. It covers a range of autonomic disorders including postural

orthostatic tachycardia syndrome (POTS), vasovagal syncope, orthostatic hypotension (OH), and undefined conditions with autonomic dysfunction(Hovaguimian, 2023). Dysautonomia may contribute to fatigue, dizziness, and other somatic symptoms commonly reported by individuals with CMP (De Wandele, Calders, et al., 2014; Mathias et al., 2021). The diagnostic criteria for common autonomic disorders is: POTS - heart rate increase ≥30 bpm within 10 minutes of standing without OH: and OH - systolic blood pressure drop of ≥20 mmHg or a diastolic drop of ≥10 mmHg within 3 minutes of standing (Freeman et al., 2011; Sheldon et al., 2015; Raj et al., 2020). The commonly used objective tests are Head Up Tilt (HUT), 10-min lean test, and adapted autonomic profile test (Sivan et al., 2022).

Dysautonomia is frequently observed in individuals with CMP and may contribute to altered pain modulation (Arslan and Ünal Çevık, 2022). Several CMP conditions are often accompanied by inflammation and oxidative stress, regulated by noradrenaline and acetylcholine, key components of the ANS (De Couck et al., 2014). However, there is a significant gap in the integration of dysautonomia into the assessment and treatment strategies for CMP, such as arthritis pain (Courties et al., 2017).

Given the significant interaction between the ANS and the musculoskeletal system, integrating dysautonomia assessment and management into the care plan for individuals with CMP has the potential to improve overall outcomes, including pain reduction. To facilitate translating this into clinical practice, we aimed to estimate the pooled prevalence of dysautonomia among individuals living with a wide range of conditions resulting in CMP.

Methods

Protocol and Registration

This systematic review was conducted in accordance with the PRISMA guidelines and prospectively registered in the PROSPERO database (registration number: CRD42024594230).

Search Strategy

A literature search was systematically conducted to explore relevant studies available in MEDLINE and EMBASE databases (accessed via OVID). The search was restricted to studies in humans only, written in the English language between 1st January 1990 to 4th October 2024. The search terms included synonyms for autonomic dysfunction, dysautonomia, CMP, and prevalence, with the full search strategy provided in Supplementary Table 1. The reference lists of the identified publications were manually searched for additional eligible studies.

Eligibility Criteria

Only studies reported in peer-reviewed publications were eligible. All relevant observational studies (i.e. case-control studies, cross-sectional studies, surveys, randomised controlled trials or cohort studies) containing adults aged 18 or above, living with inflammatory or non-inflammatory musculoskeletal conditions where persistent pain is a recognised symptom (e.g. rheumatoid arthritis or fibromyalgia) were included. Only studies reporting either standardised patient-reported screening tools or outcome tools, or validated objective measures to assess dysautonomia in CMP, were included.

We excluded any studies that did not utilise standardised outcome measures or that relied solely on continuous physiological measures (e.g. such as heart rate variability), unless they reported dysautonomia prevalence in their results. All reviews, non-peer-reviewed studies (e.g. conference posters, abstracts, or editorials) were excluded. Populations other than those with CMP were also excluded. Where study participants overlapped those from another publication, the more recent publication was selected.

Study Selection

Two independent reviewers screened titles and abstracts for relevance (NAA, DCG). Disagreements were resolved by consensus or by consulting a third reviewer (MS). Full texts were assessed for eligibility based on the predefined criteria. A PRISMA flow diagram (Figure 1) summarises the selection process, including the number of studies screened, excluded (with reasons), and included.

Data Extraction

Data were extracted using a standardized form. Information collected included study characteristics (e.g., author, year, design, sample size), diagnostic methods, and the number of confirmed cases of dysautonomia. The extracted data were checked by a second reviewer to ensure accuracy and reliability, with two reviewers participating in the extraction and validation process (NAA, DCG).

Risk of Bias Assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale(Modesti et al., 2016; Nayebirad et al., 2023). The scale evaluated domains for selection, comparability of controls, and outcome reporting (Supplemental Table 3), with a maximum total score of 7. Between 0 and 3 stars were interpreted as high risk of bias, 4 to 5 stars as moderate risk, and 6 to 7 stars as low risk.

Data Synthesis and prevalence estimation

Quantitative data on the prevalence of autonomic dysfunction were pooled using random-effects meta-analysis using the Freeman–Tukey-transformed proportion, to restrict estimates and confidence limits to within the range 0 to 100% (Freeman and Tukey, 1950). In cases where different autonomic domains or testing methods were reported separately rather than in combination, the most sensitive testing methods or outcome for detecting dysautonomia was selected for inclusion in the overall prevalence estimate. Meta-analyses were conducted (i) across all studies, (ii) within subgroups defined by autonomic outcomes, such as cardiac autonomic dysfunction, and (iii) the underlying musculoskeletal condition, such as fibromyalgia.

Data for healthy controls were obtained from included studies that reported a control group. The proportion of dysautonomia in people living with CMP chronic musculoskeletal pain was also compared with the proportion in healthy controls using random effects meta-analysis and presented as pooled estimates of the relative risk of dysautonomia.

Heterogeneity was presented as the range of estimates in Forest plots, and the proportion of total variation attributable to between-study heterogeneity quantified using the I^2 statistic. Small study effects such as publication bias were assessed using funnel plots and Egger's test, where at least 10 studies contributed to the meta-analysis.

Results

Characteristics of Included Studies

A total of 1,095 records were initially identified through systematic database and citation searching, including two studies identified through manual searching of references (Stojanovich et al., 2007; Nakamura et al., 2024). After excluding duplicates, 736 publications were screened for eligibility based on title and abstract, and 111 full texts retrieved for eligibility assessment. One publication was excluded due to potential sample overlap, as indicated by similar recruitment periods and shared authorship (Naschitz, 2003), with the later publication retained (Naschitz et al., 2006). Reasons for exclusion at the full text stage are provided in Supplementary Table 2. As illustrated in the PRISMA flowchart (Supplementary Fig. 1), this process resulted in data extraction from 17 studies included in this systematic review.

The key features of the included studies are presented in Table 1. Fibromyalgia was the most studied condition among the CMP conditions, with 13 studies on fibromyalgia (FM), 3 on Ehlers-Danlos syndrome (EDS) and one on rheumatoid arthritis (RA). A total of 1,003 patients with chronic musculoskeletal disease and 417 healthy controls were screened for dysautonomia across the different validated methods and settings. Further information

regarding participant demographics and study design characteristics is summarized in Table 2.

Risk of Bias Assessment

Three studies (18%) were identified as low risk of bias, 13 studies (76%) as moderate risk, and one study (6%) as high risk of bias. Whilst most studies met key methodological criteria, some lacked evidence of representative samples or autonomic testing covering a wide range of autonomic function (Supplementary Table 4).

Overall Prevalence

Across all 17 studies in any musculoskeletal condition assessing dysautonomia using any validated autonomic testing method, the estimated pooled prevalence of dysautonomia was 64% (95% CI: 51% to 76%; I^2=93%) (Fig. 1).

Comparison with healthy controls

Eight studies (47%) reported sufficient information to allow comparison of dysautonomia in people with CMP to healthy controls, using the same validated autonomic function tests. Individuals with CMP were more than twice as likely to exhibit symptoms of dysautonomia, with pooled risk ratio (RR) 2.28 (95% CI: 1.51 to 3.45) and low between-study heterogeneity (I^2 = 24%) (Fig. 2) showing consistency between studies.

Subgroups based on autonomic test category and underlying condition

Table 3 presents a summary of the pooled estimates of prevalence of dysautonomia in various chronic musculoskeletal conditions, stratified by test category and underlying condition.

Subgroups Based on Autonomic Test Outcomes

Dysautonomia involves a broad range of symptoms; however, the studies included in this review most reported objective orthostatic challenge tests, such as orthostatic intolerance and/or POTS. Seven studies reported the prevalence of autonomic dysfunction based on orthostatic intolerance identified through orthostatic challenge tests such as the tilt table test or the active standing test, conducted across various musculoskeletal conditions (supplementary material Fig.5). By this definition, the pooled prevalence of dysautonomia was estimated at 52% (95% CI: 37% to 67%; I^2=81%).

In four studies, dysautonomia was assessed using groups of cardiac autonomic objective tests, including cardiac autonomic dysfunction (CAD) or cardiac autonomic neuropathy (CAN). Assessments included standard or modified Ewing's reflex tests, as well as tools such as the ISAX system to evaluate cardiac autonomic regulation (supplementary material Fig.6). For the pooled analysis, all positive cases of cardiac dysregulation were considered as dysautonomia. The overall pooled prevalence was 64% (95% CI: 46% to 81%; I^2=82%). Additionally, three studies identified POTS using the tilt-table test, with a pooled prevalence of 15% (95% CI: 0%–44%; I^2=93%) (supplementary material Fig.7).

Dysautonomia Subjective assessment

Four studies reported the prevalence of dysautonomia using subjective measures, including the Autonomic Symptom Profile, Dizziness Handicap Inventory, COMPASS, and the Questionnaire of Dystonic Symptoms by Peltonen. The pooled prevalence based on these subjective assessments was higher than that from objective tests, at 86% (95% CI: 61% to 100%; I^2 = 95%). Subgroup analyses for other autonomic assessment methods are provided in the Supplementary Material.

Subgroups Based on Underlying Conditions

Fibromyalgia

Fibromyalgia was the most frequently studied condition among musculoskeletal disorders in this review. 13 studies assessed dysautonomia in fibromyalgia (Fig. 3), with a pooled prevalence of dysautonomia of 60% (95% CI: 45% to 75%; I^2=93%). When classified by assessment method, the prevalence of dysautonomia in fibromyalgia was estimated at 52% (95% CI: 39–65) when identified through objective testing (supplementary material Fig. 9). In contrast, prevalence reached 82% (95% CI: 44–100) when based on self-report measures (supplementary material Fig. 10). Limiting the analysis to fibromyalgia studies that examined orthostatic intolerance, the pooled prevalence was 48% (95% CI: 30% to 66%; I^2=81%) based on a meta-analysis of five studies (supplementary material Fig. 11).

Ehlers–Danlos syndrome

Three studies examined dysautonomia in Ehlers–Danlos syndrome, with a pooled prevalence of 84% (95% CI: 69–94), using an objective test in two studies and subjective method in the other one (supplementary material Fig *13)*. We grouped them together to enable prevalence estimation, as only these three studies were available for this condition.

In this review, only one study investigated autonomic dysfunction in an inflammatory condition (rheumatoid arthritis), so the available evidence was insufficient to calculate the prevalence of dysautonomia separately for non-inflammatory musculoskeletal conditions.

Small Study Effects and Publication Bias

For the meta-analysis of overall prevalence across all studies, the funnel plot and associated Egger's test (p=0.108) showed no evidence of asymmetry (Supplementary Fig.14). There were insufficient studies reporting dysautonomia based on orthostatic intolerance, or other cardiovascular outcomes, to evaluate potential small study effects such as publication bias for these outcomes. There was no evidence of funnel plot asymmetry for people living with fibromyalgia (Supplementary Fig.19) (p=0.342), but there were insufficient studies to evaluate potential asymmetry for comparison with healthy controls or for other subgroups.

Discussion:

This review found that neuro-cardiovascular-specific markers were the most examined features of dysautonomia within chronic musculoskeletal populations. These markers include both objective indicators and subjective symptoms related to cardiovascular autonomic function. Neuro-cardiovascular-related signs (e.g., orthostatic intolerance, orthostatic hypotension, POTS) are measurable, standardized, and provide reliable,

reproducible measures of autonomic function, making prevalence estimates more consistent and valid across studies.

Our meta-analysis estimated the pooled prevalence of dysautonomia to be over 50% of individuals living with CMP, and more prevalent than in healthy controls. These findings are broadly consistent with previous small clinical studies in specific patient groups. For instance, Galosi et al., (2022) study revealed that approximately 50% of fibromyalgia patients showed evidence of small fiber neuropathy, an indirect indicator of autonomic dysfunction. Similarly, dysautonomia was identified in 65% of females and 44% of males with hypermobile Ehlers-Danlos syndrome, further supporting the high prevalence of autonomic disturbances across related chronic musculoskeletal conditions (Ruiz Maya et al., 2021). A recent study (Novak et al., 2025) reported that 90% of patients with hypermobile Ehlers-Danlos syndrome (with pain) had autonomic failure on testing, further reinforcing the finding of our review.

While many previous reviews have discussed the qualitative aspects of dysautonomia in fibromyalgia and musculoskeletal pain, they have generally lacked quantitative synthesis or prevalence estimates (Kocyigit and Akyol, 2023; Yeater et al., 2022). Most existing studies have involved small sample sizes or focused primarily on continuous physiological measures such as heart rate variability without adequately quantifying how many of the participants meet the criteria for dysautonomia.

Inadequate identification of dysautonomia has prevented it from being recognised as a standard factor in clinical management. Our review fills this gap by contributing valuable

epidemiological data to the existing literature and offering a clearer picture of the clinical burden of dysautonomia in the CMP population, which ultimately raising clinicians' awareness to consider this condition when assessing CMP patients and manage its impact more effectively. Our review findings provide further evidence to support a recent article (Blitshteyn, 2025) calling for routine dysautonomia screening in systemic conditions.

Although our estimate is slightly higher, it may be explained and supported by physiological evidence from Bruehl et al. (2018), one of the largest population-based investigations to assess autonomic function in chronic pain. Over 1,100 participants with chronic pain were compared to 5,600 pain-free controls using HRV and baroreflex sensitivity (BRS) derived from continuous cardiovascular recordings. The results showed significantly reduced HRV and BRS in the chronic pain group, indicating dysautonomia. While this study did not quantify prevalence directly, its rigorous methodology and large sample size provide a substantial contribution to the physiological evidence base supporting the prevalence estimates reported in our meta-analysis. Together, these findings underscore the importance of routine autonomic assessment in CMP populations.

Given the autonomic nervous system's broad systemic effects, dysautonomia symptoms can be diverse, and encompassing symptoms from all systems (e.g., cardiac, somatic, gastrointestinal). This can introduce significant variation in estimated prevalence, depending on the methods used. While we have explored a number of pre-defined subgroups based on the aspects of dysautonomia assessed, and based on the type of musculoskeletal condition, substantial between-study heterogeneity remained. However, when making within-study comparisons with healthy controls, most heterogeneity was

eliminated and indicated that people with CMP were more than twice as likely to have dysautonomia.

It is worth noting that four studies in this review incorporated subjective methods to report dysautonomia prevalence within CMP, and only one of them did so in combination with objective assessments, while the remaining studies either relied solely on one objective measure or used combinations of objective tests. This underscores the limited incorporation of patient-reported outcome measures (PROMs) in the existing literature and highlights the need for future studies to include both PROMs and objective tests when investigating dysautonomia in CMP.

Across the 17 studies included in this review, only one investigated autonomic dysfunction in an inflammatory condition (rheumatoid arthritis), whereas the remaining studies focused on non-inflammatory conditions. Given the limited evidence on inflammatory conditions, a direct comparison of prevalence between inflammatory and non-inflammatory groups was not feasible, and the current evidence base is insufficient to draw firm conclusions. Future studies are warranted to address this gap.

Dysautonomia have been observed in other chronic painful conditions such as chronic fatigue syndrome and Long COVID, indicating potential shared underlying mechanisms (Garner and Baraniuk, 2019; Lee et al., 2024; Sivan et al, 2023). Early screening for dysautonomia is essential as diagnosis currently takes an average of 7.7 years (O'Dell et al., 2025). Validated patient-reported outcome measures including COMPASS-31 or SPIDER, followed by in-clinic 10-minute active standing/ lean test can facilitate early objective

detection of dysautonomia in CMP as a cost-effective screening measure. Patients whose screen positive is inconclusive can be referred to more advanced autonomic diagnostic testing such as HUT or tilt-table tests.

Management of dysautonomia may begin with non-pharmacological approaches, including lifestyle modifications such as increased fluid and salt intake, use of compression garments, avoidance of prolonged standing and high temperatures, and calf exercise programmes. Pharmacological options including beta-blockers/ ivabradine and midodrine/ fludrocortisone may be considered later if the patient response is insufficient (Mathias et al., 2011).

Limitations

Two studies by De Wandele et al. (2014) conducted at the same research centre with a potential possibility of overlapping patient cohorts. However, these studies employed different assessment methods (objective autonomic testing vs. subjective questionnaire) indicating they were separate groups.. Although potential overlap in the overall pooled estimate cannot be excluded, sensitivity analyses carried out excluding each study in turn had no influence on conclusions.

This meta-analysis is primarily based on studies of fibromyalgia, with limited data on other musculoskeletal conditions such as EDS or rheumatoid arthritis. As a result, the generalisability of the findings to broader musculoskeletal populations may be limited. We did not include hypermobility spectrum disorder or small fiber neuropathy in the conditions which restricted the search. While the pooled prevalence indicates a substantial burden, the

narrow scope of conditions and differences in autonomic testing methods may have introduced heterogeneity. Research that standardises assessment practices for people with CMP and research in rarer or less-easily investigated conditions may add further insight.

Conclusion

Dysautonomia can lead to several health challenges, including but not limited to orthostatic intolerance, cardiac dysfunction, pain and fatigue. Two-thirds of CMP patients have some degree of dysautonomia when assessed using subjective and objective tests. This highlights the importance of clinicians screening for dysautonomia and managing it appropriately within a comprehensive management plan for CMP.

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References

Anon n.d. The Declaration of Montreal | International Association for the Study of Pain. [Accessed 19 February 2025]. Available from: https://www.iasp-pain.org/advocacy/iasp-statements/access-to-pain-management-declaration-of-montreal/?utm_source=chatgpt.com.

Arslan, D. and Ünal Çevık, I. 2022. Interactions between the painful disorders and the autonomic nervous system. *Agri*. 34(3), pp.155–165.

Blitshteyn, S. 2025. Dysautonomia: a common comorbidity of systemic disease. *Immunologic research*. 73(1).

Bruehl, S., Olsen, R.B., Tronstad, C., Sevre, K., Burns, J.W., Schirmer, H., Nielsen, C.S., Stubhaug, A. and Rosseland, L.A. 2018. Chronic pain-related changes in cardiovascular regulation and impact on comorbid hypertension in a general population: The Tromsø study. *Pain*. 159(1), pp.119–127.

Chaves, A.C.S., Reis, F.J.J., Bandeira, P.M., Fernandes, O. and Arruda Sanchez, T. 2021. Autonomic dysregulation and impairments in the recognition of facial emotional expressions in patients with chronic musculoskeletal pain. *Scandinavian journal of pain*. 21(3), pp.530–538.

De Couck, M., Nijs, J. and Gidron, Y. 2014. You May Need a Nerve to Treat Pain: The Neurobiological Rationale for Vagal Nerve Activation in Pain Management. *The Clinical Journal of Pain*. 30(12).

Courties, A., Sellam, J. and Berenbaum, F. 2017. Role of the autonomic nervous system in osteoarthritis. *Best Practice & Research Clinical Rheumatology*. 31(5), pp.661–675.

El-Sawy, N., El-Tantawi, G., Achmawi, G.A.H., Sultan, H. and Younis, S. 2012. Autonomic changes in fibromyalgia: Clinical and electrophysiological study. *Alexandria Journal of Medicine*. 48(3), pp.215–222.

Freeman, M.F. and Tukey, J.W. 1950. Transformations Related to the Angular and the Square Root. *https://doi.org/10.1214/aoms/1177729756*. 21(4), pp.607–611.

Freeman, R., Wieling, W., Axelrod, F.B., Benditt, D.G., Benarroch, E., Biaggioni, I., Cheshire, W.P., Chelimsky, T., Cortelli, P., Gibbons, C.H., Goldstein, D.S., Hainsworth, R., Hilz, M.J., Jacob, G., Kaufmann, H., Jordan, J., Lipsitz, L.A., Levine, B.D., Low, P.A., Mathias, C., Raj, S.R., Robertson, D., Sandroni, P., Schatz, I., Schondorff, R., Stewart, J.M. and Van Dijk, J.G. 2011. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*. 21(2), pp.69–72.

Furlan, R., Colombo, S., Perego, F., Atzeni, F., Diana, A., Barbic, F., Porta, A., Pace, F., Malliani, A. and Sarzi-Puttini, P. 2005. Abnormalities of cardiovascular neural control and reduced

orthostatic tolerance in patients with primary fibromyalgia. *The Journal of Rheumatology*. 32(9).

Galosi, E., Truini, A. and Di Stefano, G. 2022. A Systematic Review and Meta-Analysis of the Prevalence of Small Fibre Impairment in Patients with Fibromyalgia. *Diagnostics*. 12(5), p.1135.

Garner, R. and Baraniuk, J.N. 2019. Orthostatic intolerance in chronic fatigue syndrome. *Journal of Translational Medicine*. 17(1), p.185.

Hovaguimian, A. 2023. Dysautonomia: Diagnosis and Management. *Neurologic Clinics*. 41(1), pp.193–213.

Kocyigit, B.F. and Akyol, A. 2023. Coexistence of fibromyalgia syndrome and inflammatory rheumatic diseases, and autonomic cardiovascular system involvement in fibromyalgia syndrome. *Clinical Rheumatology*. 42(3), pp.645–652.

Kulshreshtha, P., Deepak, K.K., Yadav, R.K. and Mukherjee, D. 2022. Cardiac autonomic neuropathy in fibromyalgia: Revisited. *Journal of Back and Musculoskeletal Rehabilitation*. 35(1), pp.111–117.

Lee, C., Greenwood, D.C., Master, H., Balasundaram, K., Williams, P., Scott, J.T., Wood, C., Cooper, R., Darbyshire, J.L., Gonzalez, A.E., Davies, H.E., Osborne, T., Corrado, J., Iftekhar, N., Rogers, N., Delaney, B., Greenhalgh, T. and Sivan, M. 2024. Prevalence of orthostatic intolerance in long covid clinic patients and healthy volunteers: A multicenter study. *Journal of medical virology*. 96(3).

Lee, K., Choi, S., Kang, J., Yim, Y., Kim, J., Lee, J., Wen, L., Park, D., Kim, T., Park, Y. and Lee, S. 2018. Comparison of heart rate variability and classic autonomic testing for detection of cardiac autonomic dysfunction in patients with fibromyalgia. *International Journal of Rheumatic Diseases*. 21(4), pp.804–812.

Lyng, K.D., Djurtoft, C., Bruun, M.K., Christensen, M.N., Lauritsen, R.E., Larsen, J.B., Birnie, K.A., Stinson, J., Hoegh, M.S., Palsson, T.S., Olesen, A.E., Arendt-Nielsen, L., Ehlers, L.H., Fonager, K., Jensen, M.B., Würtzen, H., Poulin, P.A., Handberg, G., Ziegler, C., Moeller, L.B., Olsen, J., Heise, L. and Rathleff, M.S. 2023. What is known and what is still unknown within chronic musculoskeletal pain? A systematic evidence and gap map. *Pain*. 164(7), pp.1406–1415.

Mathias, C.J., Low, D.A., Iodice, V., Owens, A.P., Kirbis, M. and Grahame, R. 2011. Postural tachycardia syndrome--current experience and concepts. *Nature reviews. Neurology*. 8(1), pp.22–34.

Mathias, C.J., Owens, A., Iodice, V. and Hakim, A. 2021. Dysautonomia in the Ehlers-Danlos syndromes and hypermobility spectrum disorders-With a focus on the postural tachycardia syndrome. *American journal of medical genetics. Part C, Seminars in medical genetics*. 187(4), pp.510–519.

Modesti, P.A., Reboldi, G., Cappuccio, F.P., Agyemang, C., Remuzzi, G., Rapi, S., Perruolo, E., Parati, G., Agostoni, P., Barros, H., Basu, S., Benetos, A., Ceriello, A., Prato, S. Del, Kalyesubula, R., Kilama, M.O., O'Brien, E., Perlini, S., Picano, E., Redon, J., Stuckler, D., van Bortel, L.M., Zhao, D., Bamoshmoosh, M., Bennet, L., Bruno, R.M., Carlsson, A.C., Cifkova, R., Fadnes, L.T., Grech, H., Klocek, M., Kumar, B., Lalic, N., Manolis, A.J., Nørredam, M., Massetti, L., de Courten, M.P., Pereira, M., Pratali, L., Siegert, A., Szklarska, A., Tendera, M., Twagirumukiza, M., Volodina, A., Watfa, G., Karaye, K.M., Phanzu, B.K., Dzudie, A., N'Guetta, R., Kiiza, M.C., Gudina, E.K., Longo-Mbenza, B., Mucumbitsi, J., Anisiuba, B., Ibrahim, T.A. and Okechukwu, O.S. 2016. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. *PLoS ONE*. 11(1), p.e0147601.

Mucci, V., Demori, I., Rapallo, F., Molinari, E., Losacco, S., Marinelli, L., Browne, C.J. and Burlando, B. 2022. Vestibular Disability/Handicap in Fibromyalgia: A Questionnaire Study. *Journal of Clinical Medicine*. 11(14), p.4017.

Nakamura, Y., Shibata, M., Morisaki, Y., Hirabayashi, N., Higashioka, M., Hata, J., Hosoi, M., Sudo, N., Yamaura, K. and Ninomiya, T. 2024. Autonomic nervous system function assessed by heart rate variability and the presence of symptoms affecting activities of daily living in community-dwelling residents with chronic pain: The Hisayama Study. *European Journal of Pain (United Kingdom)*. 28(5), pp.831–844.

Naschitz, J.E. 2003. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. *QJM*. 96(2), pp.133–142.

Naschitz, J.E., Mussafia-Priselac, R., Kovalev, Y., Zaigraykin, N., Elias, N., Rosner, I. and Slobodin, G. 2006. Patterns of Hypocapnia on Tilt in Patients with Fibromyalgia, Chronic Fatigue Syndrome, Nonspecific Dizziness, and Neurally Mediated Syncope. *The American Journal of the Medical Sciences*. 331(6), pp.295–303.

Nayebirad, S., Mohamadi, A., Yousefi-Koma, H., Javadi, M., Farahmand, K., Atef-Yekta, R., Tamartash, Z., Jameie, M., Mohammadzadegan, A.M. and Kavosi, H. 2023. Association of anti-Ro52 autoantibody with interstitial lung disease in autoimmune diseases: a systematic review and meta-analysis. *BMJ Open Respiratory Research*. 10(1).

Novak, P., Systrom, D.M., Marciano, S.P., Witte, A., Warren, A., Felsenstein, D., Giannetti, M.P., Hamilton, M.J., Nicoloro-SantaBarbara, J., Castells, M., Farhad, K., Pilgrim, D.M., Mullally, W.J., Fishman, M.C., Milunsky, J.M., Milunsky, A. and Krier, J. 2025. Hypermobile Ehlers-Danlos Syndrome: Cerebrovascular, Autonomic and Neuropathic Features. *American Journal of Medicine Open*. 14.

Oaklander, A.L., Herzog, Z.D., Downs, H.M. and Klein, M.M. 2013. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain*. 154(11), pp.2310–2316.

O'Dell, J.A., Walker, A., Latham, A.J., Parisian, D.J., Branch, L.E., Vanderburg, D.D., Cox, A.A., Chavis, S. and Smith, S.E. 2025. The Diagnostic Journey of Dysautonomia Patients: Insights from a Patient-Reported Outcome Study. *Journal of patient experience*. 12.

Raj, S.R., Guzman, J.C., Harvey, P., Richer, L., Schondorf, R., Seifer, C., Thibodeau-Jarry, N. and Sheldon, R.S. 2020. Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance. *Canadian Journal of Cardiology*. 36(3), pp.357–372.

Ruiz Maya, T., Fettig, V., Mehta, L., Gelb, B.D. and Kontorovich, A.R. 2021. Dysautonomia in hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders is associated with exercise intolerance and cardiac atrophy. *American journal of medical genetics. Part A*. 185(12), p.3754.

Rundell, S.D., Patel, K. V., Krook, M.A., Heagerty, P.J., Suri, P., Friedly, J.L., Turner, J.A., Deyo, R.A., Bauer, Z., Nerenz, D.R., Avins, A.L., Nedeljkovic, S.S. and Jarvik, J.G. 2019. Multi-site Pain Is Associated with Long-term Patient-Reported Outcomes in Older Adults with Persistent Back Pain. *Pain Medicine (United States)*. 20(10), pp.1898–1906.

Seidel, M.F., Weinreich, G.F., Stratz, T. and Müller, W. 2007. 5-HT3 receptor antagonists regulate autonomic cardiac dysfunction in primary fibromyalgia syndrome. *Rheumatology International*. 27(11), pp.1025–1030.

Sheldon, R.S., Grubb, B.P., Olshansky, B., Shen, W.K., Calkins, H., Brignole, M., Raj, S.R., Krahn, A.D., Morillo, C.A., Stewart, J.M., Sutton, R., Sandroni, P., Friday, K.J., Hachul, D.T., Cohen, M.I., Lau, D.H., Mayuga, K.A., Moak, J.P., Sandhu, R.K. and Kanjwal, K. 2015. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 12(6), pp.e41–e63.

Singh, R., Rai, N.K., Rastogi, A., Endukuru, C., Joshi, A. and Mishra, S.S. 2021. Impact of sleep disturbances and autonomic dysfunction on the quality of life of patients with fibromyalgia. *Journal of Basic and Clinical Physiology and Pharmacology*. 32(6), pp.1021–1029.

Sivan, M., Corrado, J. and Mathias, C. 2022. The adapted Autonomic Profile (aAP) home-based test for the evaluation of neuro-cardiovascular autonomic dysfunction. *Advances in Clinical Neuroscience & Rehabilitation*. 21(3), pp.10–13.

Sivan, M., Mckeever, V., Natt, M. and Newton, J. 2023. A global need for more awareness of dysautonomia in postviral syndromes. *Journal of medical virology*. 95(8).

Solano, C., Martinez, A., Becerril, L., Vargas, A., Figueroa, J., Navarro, C., Ramos-Remus, C. and Martinez-Lavin, M. 2009. Autonomic Dysfunction in Fibromyalgia Assessed by the Composite Autonomic Symptoms Scale (COMPASS). *JCR: Journal of Clinical Rheumatology*. 15(4), pp.172–176.

Song, B., Yeh, P. and Harrell, J. 2021. Systemic manifestations of Ehlers-Danlos syndrome. *Baylor University Medical Center Proceedings*. 34(1), pp.49–53.

Stojanovich, L., Milovanovich, B., De Luka, S.R., Popovich-Kuzmanovich, D., Bisenich, V., Djukanovich, B., Randjelovich, T. and Krotin, M. 2007. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus*. 16(3), pp.181–185.

Tang, S. 2004. Neurally mediated hypotension in systemic lupus erythematosus patients with fibromyalgia. *Rheumatology*. 43(5), pp.609–614.

Treede, R.D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., Giamberardino, M.A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'Homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B.H., Svensson, P., Vlaeyen, J.W.S. and Wang, S.J. 2019. Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 160(1), pp.19–27.

Treede, R.D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., Giamberardino, M.A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B.H., Svensson, P., Vlaeyen, J.W.S. and Wang, S.J. 2015. A classification of chronic pain for ICD-11. *Pain*. 156(6), pp.1003–1007.

Vincent, A., Whipple, M.O., Low, P.A., Joyner, M. and Hoskin, T.L. 2016. Patients With Fibromyalgia Have Significant Autonomic Symptoms But Modest Autonomic Dysfunction. *PM&R*. 8(5), pp.425–435.

Visuri, T., Lindholm, H., Lindqvist, A., Dahlström, S. and Viljanen, A. 1992. Cardiovascular functional disorder in primary fibromyalgia. A noninvasive study in 17 young men. *Arthritis & Rheumatism*. 5(4), pp.210–215.

De Wandele, I., Calders, P., Peersman, W., Rimbaut, S., De Backer, T., Malfait, F., De Paepe, A. and Rombaut, L. 2014. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls. *Seminars in Arthritis and Rheumatism*. 44(3), pp.353–361.

De Wandele, I., Rombaut, L., Leybaert, L., Van de Borne, P., De Backer, T., Malfait, F., De Paepe, A. and Calders, P. 2014. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Seminars in Arthritis and Rheumatism*. 44(1), pp.93–100.

Welsh, T.P., Yang, A.E. and Makris, U.E. 2020. Musculoskeletal Pain in Older Adults: A Clinical Review. *The Medical clinics of North America*. 104(5), pp.855–872.

Yeater, T.D., Clark, D.J., Hoyos, L., Valdes-Hernandez, P.A., Peraza, J.A., Allen, K.D. and Cruz-Almeida, Y. 2021. Chronic Pain is Associated With Reduced Sympathetic Nervous System Reactivity During Simple and Complex Walking Tasks: Potential Cerebral Mechanisms. *Chronic Stress*. 5, p.24705470211030270.

Yeater, T.D., Cruz, C.J., Cruz-Almeida, Y. and Allen, K.D. n.d. *Autonomic Nervous System Dysregulation and Osteoarthritis Pain: Mechanisms, Measurement, and Future Outlook* [Online]. Available from: https://www.springer.com/journal/11926.

Study (Author, Year)	Country	Setting	Medical diagnosis	Sample size	Age means	Female n	Control group	Age means	Method used	
									Subjective methods	Objective methods
(De Wandele, Calders, et al., 2014)	Belgium	hospital	Ehlers-Danlos syndrome	80	41	75	0		Autonomic symptom profile	
(De Wandele, Rombaut, et al., 2014)	Belgium	hospital	Ehlers-Danlos syndrome	39	39	39	35	40		Tilt table test
(El-Sawy et al., 2012)	Egypt	hospital	Fibromyalgia	25	37	23	0			Tilt table test and Sympathetic skin response
(Furlan et al., 2005)	Italy	hospital	Fibromyalgia	16	44	15	16	37		Tilt table test
(Kulshreshtha et al., 2022)	India	hospital	Fibromyalgia	42	398	42	0			Modified Ewing's battery
(Lee et al., 2018)	South Korea	hospital	Fibromyalgia	35	42	35	25	42 (±5 years)		Ewing's battery
(Mucci et al., 2022)	Italy	community	Fibromyalgia	277	48	248	80	47	Dizziness Handicap level	
(Naschitz et al., 2006)	Israel	hospital	Fibromyalgia	70	45	0	50	30		Tilt table test
(Oaklander et al., 2013)	Massachusetts	community	Fibromyalgia	27	47	20	30	45		Autonomic-function testing (AFT)
(Seidel et al., 2007)	Germany	hospital	Fibromyalgia	72	49	72	36	49		Autonomic cardiac dysregulation - ISAX device
(Singh et al., 2021)	India	hospital	Fibromyalgia	30	39	27	30	38		Ewing's battery
(Solano et al., 2009)	Mexico	hospital	Fibromyalgia	30	47	30	30	39	Composite Autonomic Symptom Scale	
(Song et al., 2021)	USA	hospital	Ehlers-Danlos syndrome	98	38	94	0			Clinical diagnosis of Autonomic dysfunction
(Stojanovich et al., 2007)	Serbia	hospital	Rheumatoid arthritis	39	58	33	35	52		Active standing test Ewing's battery of tests
(Tang, 2004)	USA	hospital	Fibromyalgia	76	40	72	0			Tilt table test
(Vincent et al., 2016)	USA	community	Fibromyalgia	30	47	30	30	41		Composite Autonomic Scoring Scale
(Visuri et al., 1992)	Finland	hospital	Fibromyalgia	17	20	0	20	21	Questionnaire of dystonic symptoms by Peltonen	Active standing test

Table 1 Summary of All Included Studies

Table 2 Descriptive Summary of Study Populations and Methodological Characteristics

Section	***Category***	***N (%)***	***Participants N***
Study Overview	Total studies included	17	1003
	Fibromyalgia	13 (77%)	747
	Ehlers-Danlos syndrome	3 (18%)	217
	Rheumatoid arthritis	1 (5%)	39
Participant Demographics	Mean age of participants	42.29	
	Chronic musculoskeletal participants	1003	
	Control group participants	252	
	Female (Chronic MSK participants)	855 (85%)	
	Female (Controls)	140 (56%)	
Assessment Methods	Studies including orthostatic challenge tests	7 (41%)	
	Studies including cardiac autonomic function tests	7 (41%)	
	Studies including other specific/mixed tests	6 (35%)	
	Studies including subjective measures	4 (24%)	
Study Setting	Hospital-based studies	14 (82%)	
	Community-based studies	3 (18%)	

Table 3 Prevalence of Dysautonomia in Chronic Musculoskeletal Conditions: Stratified by Test category and Underlying Diagnosis

Test category	*Across various* ***MSK Conditions (FM, RA, EDS)***	***FM***
All measures,	n= 17 64% (95% CI 51, 76) I^2 = 93%	n= 13 60% (95% CI 45, 75) I^2 = 93%
All objective,	n=13 56% (95% CI 44, 67) I^2= 87%	n= 11 52% (95% CI 39, 65) I^2 = 85%
All subjective	n=4 86% (95% CI 61, 100) I^2 = 95	n=3 82% (95% CI 44,100) I^2 = 95%

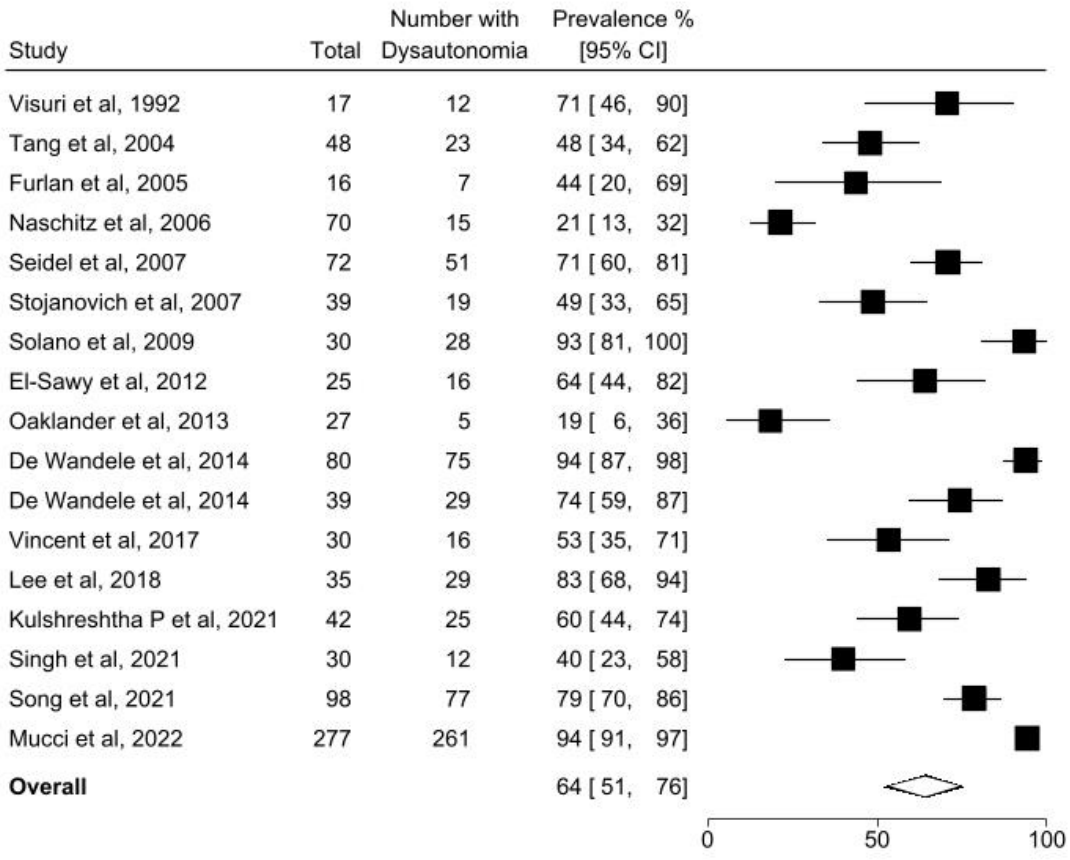

Figure 1 caption: Forest plot shows overall pooled prevalence estimates of dysautonomia in all included musculoskeletal conditions using validated objective and subjective methods

Alt text: Forest plot with 17 studies showing prevalence ranging from 19 to 94 percent, individual estimates as squares with confidence intervals, and pooled estimate of 64 percent as diamond.

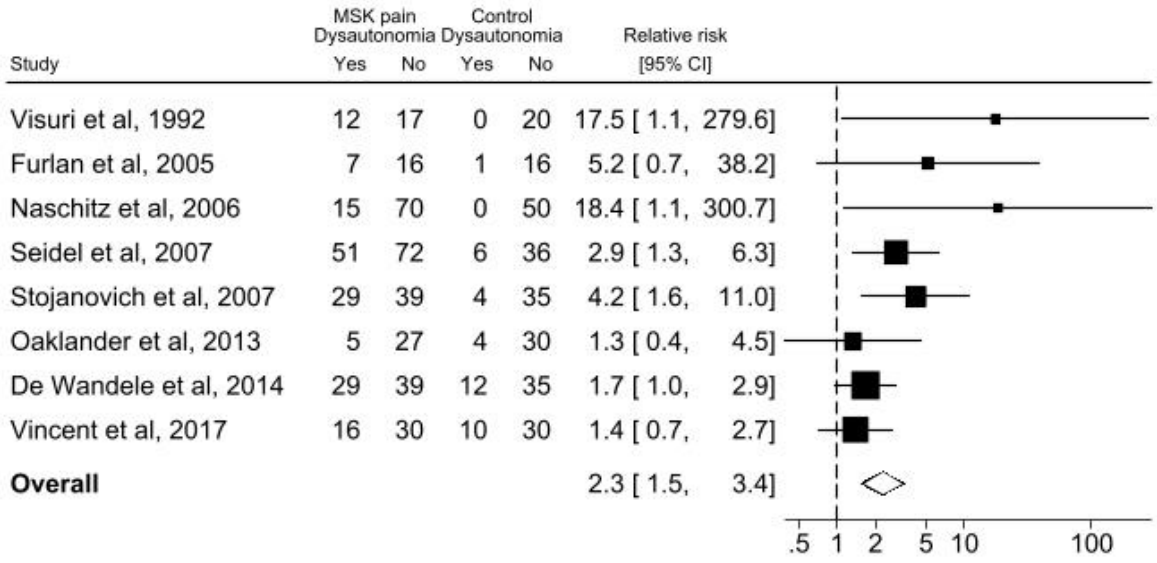

Figure 2 Forest plot of 8 studies comparing dysautonomia in MSK pain patients vs. healthy controls. Pooled RR = 2.3 (95% CI: 1.5–3.4); I^2 = 24.35% (random-effects model).

Alt: Forest plot with eight studies displaying risk ratio estimates as squares with horizontal confidence interval lines, showing consistently elevated risk of dysautonomia in patient group compared to controls.

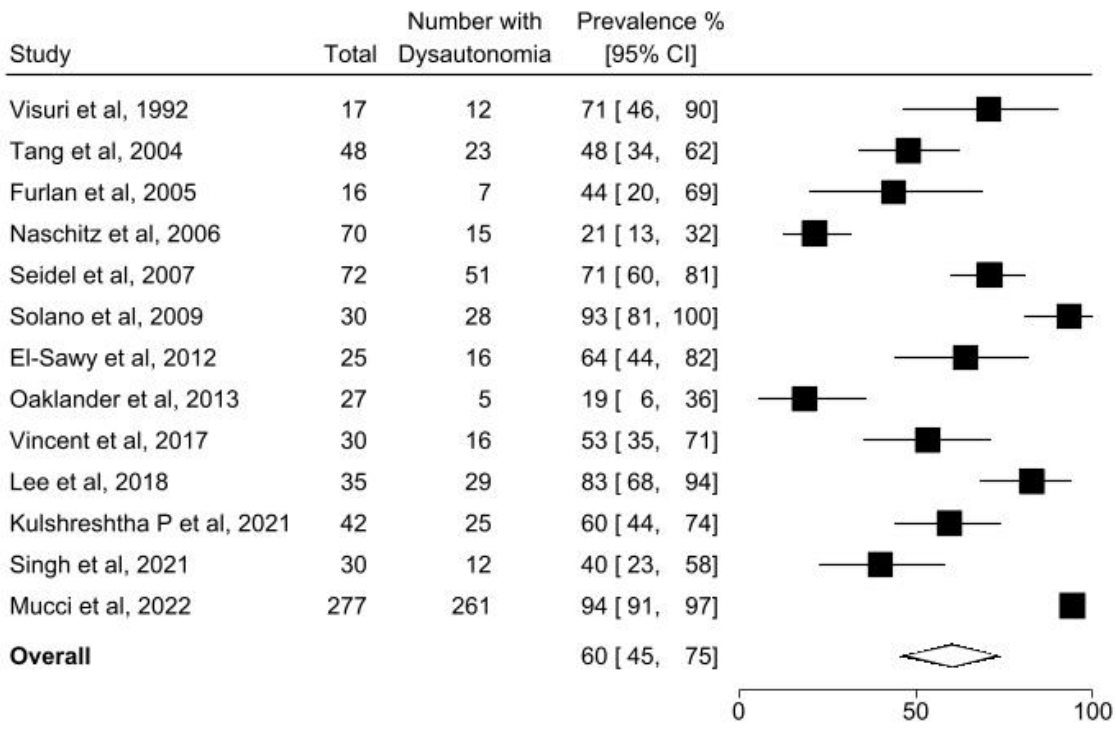

Figure 3 Forest plot shows overall pooled prevalence estimates of dysautonomia in fibromyalgia using validated objective and subjective methods

Alt: Forest plot displaying 13 fibromyalgia studies with prevalence estimates ranging from 19 to 94 percent, individual results shown as squares with confidence intervals and pooled diamond at bottom.