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Review article

Sex adjusted standardized prevalence ratios for celiac disease and other autoimmune diseases in patients with postural orthostatic tachycardia syndrome (POTS): A systematic review and meta-analysis

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A B S T R A C T

Standardised sex-adjusted prevalence ratios (SSPRs) have not been published for any autoimmune diseases (ADs) in patients with Postural Orthostatic Tachycardia Syndrome (POTS), who are predominantly young females. We performed a systematic review according to PRISMA guidelines of POTS cohorts reporting the prevalence of at least one AD. Only four studies were found: two providing data on celiac disease; and two with data on 'any AD', Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome and celiac disease and (one study) antiphospholipid syndrome. All studies were assessed as being at high risk of bias for estimating AD prevalence in POTS patients, with under-reporting of ADs likely due to the lack of rigorous prospective screening for ADs. A literature search found a 'gold standard' general population (GP) comparator only for celiac disease in the United States, leading to a pooled SSPR in POTS patients of 2.75 with 95% confidence interval (1.06–4.40). The lack of recent high-quality studies on GP prevalence for the other ADs was noteworthy. Exploratory pooled SSPRs were calculated for 'any AD' and for the other five ADs using GP comparator data from a comprehensive review. All pooled SSPRs were greater than one and statistically significant, implying a higher prevalence of these ADs, and any AD, in POTS patients. The magnitude of the exploratory SSPRs was very large for SLE, Sjögren's syndrome and antiphospholipid syndrome, perhaps reflecting the use of non-gold standard GP comparators, which may underestimate AD prevalence. Further research in a large POTS cohort with an appropriately age- and sex-matched GP control group is recommended, to confirm the SSPR for celiac disease and to determine whether SLE, Sjogren's syndrome and antiphospholipid syndrome are indeed many times more prevalent in POTS patients than in the GP. The findings are consistent with POTS itself being an AD.

1. Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is an under-recognised disorder which mainly affects young woman of childbearing age. The symptoms include light headedness, fatigue, palpitations, pre-syncope, sleep disturbances, cognitive impairment and brain fog in conjunction with an exaggerated increase in heart rate when upright, despite maintenance of a normal blood pressure [1]. The prevalence of POTS is unknown but is estimated to be between 0.1 and 1% in the US population [2]. Although orthostatic tachycardia is pivotal in its diagnosis, POTS is frequently a multisystem disorder [3] and can impair activities of daily living, sometimes as severely as other conditions such as chronic obstructive pulmonary disease and congestive heart failure [1].

The aetiology is uncertain, but the hypothesis that, in some patients at least, POTS may be an autoimmune disease (AD) is currently being tested [4]. Patients with one AD are often more prone to others. A review of autoimmunity in POTS by Ref. [5] found that

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"patients with POTS have a higher than expected frequency of defined autoimmune disorders such as multiple sclerosis, lupus, Sjögren syndrome or celiac disease". This conclusion was based on several case series and two retrospective chart reviews each carried out in 100 POTS patients by Refs. [6,7] and a self-reported survey of 4835 POTS patients by Ref. [3].

There is abundant literature documenting a high rate of misdiagnosis and lengthy diagnostic delays for ADs [8,9]; Bunya et al., 2019 [10], hence any study reporting autoimmunity in POTS that is not prospective with uniform and methodical screening for a defined list of ADs would likely significantly under-report the actual rate of these conditions in POTS patients.

Moreover, despite POTS being a disorder primarily occurring in women, and many ADs having an uneven prevalence in the two sexes, we are not aware of any estimates of standardised sex-adjusted prevalence ratios of ADs in POTS patients.

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [11] our aim was first to systematically search for other cohorts ($n \geq 100$) of POTS patients which included data on comorbid ADs. We sought next to assess the risk of bias of these and the three existing cohorts [6, 7], and [3]. Next, we hoped to calculate sex adjusted standardized prevalence ratios (SSPRs) and associated 95% confidence intervals for the various ADs in POTS patients using reliable GP prevalence estimates from the recent literature.

Finally, we planned to report pooled SSPRs for ADs where appropriate, according to the PRISMA checklist in Ref. [11]. Thus, we hoped to provide the best estimates available of SSPRs in POTS patients relative to the GP, given the current evidence base in the published literature in English.

2. Methods

2.1. Protocol/Registration

A protocol was not registered for this systematic review, nor was the review itself registered.

2.2. Studies eligible for inclusion in the review

Studies written in English on cohorts of at least 100 patients with POTS that reported data on the number of patients having a particular AD (or the number of patients having any AD) were eligible. ADs were any of the 81 ADs listed in Ref. [12].

2.3. Information sources, search criteria, study selection and data extracted

A literature search was carried out in PUBMED, SCOPUS and EMBASE using terms ('POTS' AND 'Postural') AND ('cohort' OR 'survey' OR 'observational' OR 'randomized'). Abstracts of these studies were then examined by one of the authors (CP) to determine whether the study included at least 100 POTS patients. For studies meeting this criterion, the abstracts, and where required, full texts, were examined by CP to find those that recorded autoimmune comorbidities for the participants. For such studies, data was extracted on the total number of POTS patients, recruitment and inclusion criteria for POTS used in the study, the criteria used to classify a study participant as having an AD, the number of cases reported of 'any AD' and of individual ADs. For studies which compared the prevalence of an AD in the study population with that in the GP, calculated odds ratios were recorded and the references for the GP comparator studies obtained if available.

2.4. Risk of bias of individual studies

A modified version of [13]'s criteria for assessing overall risk of bias for prevalence studies was used in which two more criteria were added to the existing ten criteria. These were criterion 1a): Whether an acceptable case definition of POTS was used in the study and criterion 10a): Whether key confounders such as age and sex were adjusted for in the analysis [13].'s criteria included: representativeness of the target population; representativeness of the sampling frame; random selection of sample or use of census; minimal non-response bias; direct collection of data from subjects; acceptability of the case definition of AD; reliability and validity of the study instrument used; same mode of data collection for all subjects; appropriateness of the length of the shortest prevalence period and appropriateness of the numerator and denominator. Of note, for all 10 criteria given in [13] there is only a dichotomy of responses available: either Low or High Risk of Bias.

2.5. GP prevalence estimates

We searched for recent reliable data on US GP prevalence of ADs/any AD, since the [6] study was entirely of US patients, and the majority of patients in Ref. [3] were in the US. This was done by searching PUBMED, using '(National Health and Nutrition and Examination Survey OR NHANES)' AND 'prevalence' AND the name of the AD for studies based on NHANES data collected between 2009 and 2015. We judged NHANES data to be the most reliable source of US GP data.

Data on GP prevalence of ADs in toto and on prevalence of individual ADs and the percentage female for each condition was also obtained from a comprehensive review by Ref. [12].

The US GP prevalence per 100,000 women and prevalence per 100,000 men were calculated using the assumption that the US adult population in the years 2012–2017 was 50.6% female, according to data from the US Census Bureau.

The literature was also searched for estimates of the GP prevalence of celiac disease in the UK, for use as a comparator with the [7]

cohort, which was an English study.

The UK GP prevalence per 100,000 women and prevalence per 100,000 men were calculated using the assumption that the UK adult population in the year 2011 was 50.9% female, according to data from the UK Office for National Statistics.

2.6. Summary measure - calculation of SSPR

For each AD, the expected number of prevalent cases was estimated by multiplying the study population size for each sex by the disease rate in the GP for that sex and summing the expected male and female cases to give a total expected number of cases. The observed number of prevalent cases was compared with this to give an SSPR according to equation (1) below:

$$SSPR = \frac{Total\ observed\ number\ of\ prevalent\ cases}{Total\ expected\ number\ of\ prevalent\ cases} \quad (1)$$

If the SSPR ratio was greater than 1, then the study population had excess prevalent cases compared with the GP, and vice versa. The 95% confidence interval of the SSPR was calculated by the Mid-P exact test as it is the preferred method [14]. We used an online version of OpenEpi to perform this calculation [15].).

2.7. Pooling of data

Since the review identified only a small number of studies, the meta-analysis was also based on a small number of studies. At least two studies are sufficient to perform a fixed effects meta-analysis, provided that those studies can be meaningfully pooled and provided their results are sufficiently similar. If the results were inconsistent for any study (we found this for celiac disease), then the pooled estimate was calculated by excluding the study with an inconsistent result as this was likely to introduce bias if included in the meta-analysis. Random effects meta-analysis was inappropriate because it requires at least five studies while we had two to four studies. The pooled SSPRs were obtained using weighted averages with the weights being inversely proportional to the variance (known as the inverse variance method). The pooled 95% confidence intervals for SSPRs were also calculated using the inverse variance method. SAS 9.4 was used to perform all meta analyses (SAS) [16].

Table 1
Details of included studies.

Study	Number of POTS patients	Study type	% female	Age/years	AD reported upon (number of patients with AD)
[6]	100	Retrospective chart review of consecutive POTS patients attending a US Neurology clinic between October 2012 and March 2013. All patients were tested for serum antinuclear antibodies. Presence of an AD was determined by chart review and AD diagnoses were verified with the treating physician.	91%	Mean 32 (range 13–54)	• Any autoimmune condition (20) • Hashimoto's thyroiditis (11) • Celiac disease (3) • Sjögren's syndrome (2) • Rheumatoid arthritis (4) • Systemic Lupus Erythematosus (2) • Antiphospholipid Syndrome (5)
[3]	3933	Online self-reported survey of 4830 POTS patients advertised through the website and Facebook page of the not-for-profit organisation Dysautonomia International between July 2015–July 2017. 82% of respondents were US-based. Of those surveyed, 3933 self-reported their comorbidities, including certain ADs.	94%	Mean age not reported. 88% were aged 18 or older. Mean age of symptom onset 20.7	• Any autoimmune condition (616) • Hashimoto's thyroiditis (228) • Celiac disease (133) • Sjögren's syndrome (112) • Rheumatoid arthritis (93) • Systemic Lupus Erythematosus (81)
[7]	100	Retrospective chart review of 100 POTS patients attending an out- patient clinic in the UK between May 2013–May 2015. Purpose of study was to see whether a relationship existed between gluten sensitivity and POTS. Results were compared with medical records of 1200 people without POTS from primary care practices in the same county.	84%	Median age 27 Interquartile range (22–37)	• Celiac disease (4)
[17]	332	Retrospective chart review of POTS patients attending Mayo clinic US between January 2010–January 2017. Purpose of study was to determine factors associated with requirement for non-oral nutrition.	88.6%	Mean age 29.3	• Celiac disease (7)

2.8. Risk of bias across studies

In such a meta-analysis the estimate of heterogeneity from data is likely to be unreliable, hence we did not perform any statistical test for heterogeneity across studies, but instead assessed this using a Forest plot. We planned to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, as appropriate, given the known limitations of these methods. However, with such a small number of studies, all the methods for possible detection of publication bias were underpowered, so publication bias was not assessed. Even without using these methods it is clear that the small sample size of [6] and the finding of only two patients with Sjögren's syndrome and two with SLE in that study led to imprecise estimated SSPRs (wide confidence intervals) for these conditions resulting in imprecise pooled estimates by meta-analysis.

3. Results

3.1. Studies included

The search of PUBMED, SCOPUS and EMBASE carried out on 19th July 2020 using the selection criteria detailed above resulted in 52 studies of which 18 included at least 100 POTS patients. Four studies were found that included data on at least one AD. Three of these were [6–3]; that had already been identified in Ref. [5]. One additional study by Ref. [17] was found: a retrospective chart review of 332 POTS patients attending the Mayo clinic, US. The purpose of [17]'s study was to determine factors associated with requirement for non-oral nutrition. It was mentioned that seven POTS patients (2.1%) had celiac disease. Full details of the four included studies are given in Table 1 [3,6,7,17].

The studies had data on the prevalence in POTS patients for the following ADs: Any autoimmune condition, 2 studies; Hashimoto's thyroiditis, 2 studies; celiac disease, 4 studies; Sjögren's syndrome, 2 studies; rheumatoid arthritis, 2 studies; systemic lupus erythematosus, 2 studies; antiphospholipid syndrome, 1 study.

3.2. Risk of bias within studies

These results are shown in Table 2 [3,6,7,17]. Using the modified risk of bias tool for prevalence studies in Ref. [13] we judged that their criterion 1 (Was the study's target population a close representation of the national population of POTS patients?) to be met only for [3] principally because this was an online survey launched through Dysautonomia International's website and Facebook page and thus was available to POTS patients across the US. All the other studies were judged at high risk of bias because their target populations

Table 2
Assessment of risk of bias of individual studies in providing a POTS prevalence estimate
(Using the tool from (Hoy, Brooks et al., 2012) with two additional questions (1a and 10a)
For all questions YES = LOW RISK, NO = HIGH RISK.

Criterion #	Criterion	[6]	[3]	[7]	[17]
1	Was the study's target population a close representation of the national POTS population in relation to the relevant variables e.g. age, sex? In other words was the study free from selection bias?	No, HIGH	Yes, LOW	No, HIGH	No, HIGH
1a)	Was an acceptable case definition of POTS used in the study?	Yes, LOW	No, HIGH	Yes, LOW	Yes, LOW
2	Was the sampling frame a true or close representation of the target population?	Yes, LOW	Yes, LOW	Yes, LOW	Yes, LOW
3	Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes, LOW	No, HIGH	No, HIGH	Yes, LOW
4	Was the likelihood of non-response bias minimal?	Yes, LOW	No, HIGH	No, HIGH	Yes, LOW
5	Were data collected directly from the subjects (as opposed to a proxy)?	Yes, LOW	Yes, LOW	Yes, LOW	Yes, LOW
6	Was an acceptable case definition for autoimmune disease used in the study?	No, HIGH	No, HIGH	No, HIGH	No, HIGH
7	Was the study instrument that measured the parameter of interest (autoimmune disease) shown to have reliability and validity (if necessary)?	No, HIGH	No, HIGH	No, HIGH	No, HIGH
8	Was the same mode of data collection used for all subjects?	Yes, LOW	Yes, LOW	Yes, LOW	Yes, LOW
9	Was the length of the shortest prevalence period for the parameter of interest appropriate?	No, HIGH	No, HIGH	No, HIGH	No, HIGH
10	Were the numerator(s) and denominator(s) for the parameter of interest appropriate? (ie was a mistake made, or was the denominator 100)	Yes, LOW	Yes, LOW	Yes, LOW	Yes, LOW
10a)	Were key confounders adjusted for in the analysis?	No, HIGH	No, HIGH	No, HIGH	No, HIGH
11	OVERALL STUDY RISK OF BIAS: Low risk - Further research is very unlikely to change our confidence in the estimate. Moderate risk - Further research is likely to have an important impact on our confidence in the estimate and may change it. High risk - Further research is very likely to have an important impact on our confidence in the estimate and is likely to change it.	**High risk**	**High risk**	**High risk**	**High risk**

were patients at a particular clinic, which introduced risk of bias due to geography, degree of POTS severity, and the reputation and specialism of the treating clinician(s).

Criterion 1a (Was an acceptable case definition of POTS used in the study?) was judged to be met for the three retrospective chart reviews, but not for [3]; in which POTS patients were defined as those who had received a physician's diagnosis of the condition. For Criterion 2 (Was the sampling frame a true or close representation of the target population?) we judged all of the studies at clinics using such a sampling frame (the list of POTS patients attending the clinic) as did the sampling frame for [3] which was people with POTS using Dysautonomia International's online content.

Criterion 3 (Was random sampling or a census carried out?) was judged to be at high risk of bias for [7]; in which the rationale behind the choice of 100 patients was not given, but not for the other two clinical studies which were census studies. In Ref. [3] participants were self-selected, so this was judged at high risk of bias. For criterion 4 (Was the likelihood of non-response bias minimal?) we judged [3] to be at high risk of bias because a survey response rate was not reported, and [7] was also considered at high risk of bias as how the 100 patients were selected was also not reported.

Criterion 5 (Was data collected directly from the subjects?) was met for all four studies, putting them at low risk of bias in this regard. For Criterion 6 (Was an acceptable case definition for autoimmune disease used in the study?) we noted the possibility that a majority of the POTS subjects in each study were not prospectively screened for ADs, and that all studies relied on prior diagnoses of the various ADs by a range of clinicians with no case definitions provided in Refs. [3,17]. Although [6] gave some details of the case definition used for antiphospholipid syndrome (the Sapporo criteria) it is unclear which version of these criteria was used, and, similarly, despite all cases of celiac disease "being confirmed by intestinal biopsy" no case definition is given for this or for the other ADs [7]. perhaps come closest to giving a case definition (for celiac disease), but even this is not completely clear.

Criterion 7 (Was the study instrument used to measure AD shown to have reliability and validity?) was assessed as No, High Risk for all four studies as [3] did not report on reliability or validity of their survey, while the other three studies were chart reviews, with no reports on the reliability or validity of the review process given. Criterion 8 (Was the same mode of data collection used for all subjects?) was satisfied for all four studies.

For Criterion 9 (Was the length of the shortest prevalence period for the parameter of interest (an AD diagnosis) appropriate?), none of the studies made clear the period during which an AD diagnosis was recorded, hence a high risk of bias was assumed for all studies. Criterion 10 (Were the numerators and denominators for AD prevalence estimates appropriate?) was met by all studies. Criterion 10a (Whether key confounders such as sex and age were adjusted for in the analysis?) was not met by any of the studies.

We also judged the summary risk of bias to be high for all the four studies (Criterion 11), considering particularly that none of the studies were screened prospectively for AD in POTS patients. According to Ref. [13]; high risk of bias overall means "further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate".

Of note, this assessment of bias dealt simply with bias arising in using the number of AD cases per number of POTS patients recorded in the study as an estimate of prevalence of the AD in the POTS population. Further bias would potentially be introduced if this prevalence were then compared with a GP prevalence to give an odds ratio, as was done in Refs. [6,7].

3.3. Additional risk of bias introduced through use of a GP comparator

[6] calculated odds ratios using estimates of GP prevalence for six ADs, and for 'any AD' and [7] used prevalence of celiac disease in a comparator cohort to calculate an odds ratio for celiac disease prevalence in POTS patients.

Of [6]'s GP comparators, only [16]; used for celiac disease, used NHANES data from a period (2009–10) close in timing to her measurements (made between 2012–13). We regarded this study as being 'gold standard' and at low risk of bias. No other studies used by Ref. [6] as GP comparators were based on contemporaneous NHANES data (details in Supplementary Table 1). Hence, with the exception of celiac disease, the calculation of odds ratios in Blitshteyn's study likely introduced additional risk of bias.

The comparator used by Ref. [7] was [18] which provided a GP prevalence based on an analysis of medical records of 1200 patients from five primary care practices in the same UK county, but at an earlier time period (1999–2001) than [7]'s POTS cohort, for which measurements were made in 2015. The use of a GP comparator with data from a different period is likely to increase risk of bias.

3.4. Comparator studies giving GP prevalence

To facilitate calculation of SSPRs, we searched for studies giving GP prevalence estimates for the various ADs using PUBMED, searching using 'prevalence' AND the AD name. We discovered that the literature varied widely on GP prevalence estimates for individual ADs (Table 1 supplementary material). For example, the US prevalence of Sjögren's syndrome was almost 10-fold greater in a study by Ref. [19] than it was in Ref. [12] (139 vs 14 per 100,000).

In the face of such inconsistent GP prevalence reports, we judged that data from NHANES collected as close as possible to the 2012–2017 period in which data was obtained for the four selected POTS studies (Table 1) would provide 'gold standard' US GP prevalence estimates. Only one such study was found by PubMed search on 28 March 2021. This was [20] which drew on NHANES data for 2009–10 and 2011–12 and gave the prevalence of celiac disease among US Whites as 1.08% based on measurements of two serum autoantibodies. Since 93% of the nearly 4000 POTS patients in Ref. [3] were White, using an estimated prevalence in Whites was considered preferable to using a prevalence in the whole US population. Hence, a pooled analysis was performed of the three US studies that reported celiac disease cases using [20] as the GP comparator. However [20], did not state the proportion of females having celiac disease, so the value of 57% from Ref. [16] was used as this was also based on 2009-10 NHANES data.

No suitable NHANES GP prevalence data was found for any other AD, or for 'any AD'.

Because [7] was a UK study we used [21], a UK study found in our PubMed comparator search, as the GP comparator.

To calculate 'exploratory' SSPRs for other ADs and 'any AD', GP prevalence estimates from Ref. [12] were used. This had the advantage of all the GP comparison data coming from one source which, to the best of our knowledge, was the most recent comprehensive review on the topic. Not only did this give US (or, occasionally, world) GP prevalence estimates but estimates of the proportion of females for each AD were also provided, which enabled calculation of SSPRs.

3.5. Standardised sex-adjusted prevalence ratios for comorbid ADs in POTS patients

Calculated SSPRs for each AD by study and for 'any AD' are shown in Table 3 [6,7,3,12,17,20,21], with 95% confidence intervals.

All the SSPRs calculated in all four studies for all ADs, and for 'any AD', were greater than 1 and all but two were statistically significant. Hence, for all except these two results, there was a significantly greater prevalence of the AD in POTS patients than in the GP. The exceptions were SSPRs calculated for celiac disease using data from Refs. [6,17] which, although greater than 1, had a 95% confidence interval that included 1.

For celiac disease, results from four studies (3 from the US and 1 from the UK) were available, as was a 'gold standard' GP comparator that was appropriate for the US-based studies. The SSPR for celiac disease of 12.73 calculated using [7] with [21] as GP prevalence comparator did not lie within the confidence intervals of any of the SSPRs calculated from the three US studies. This was due in the main to a much lower GP prevalence of celiac disease in the UK GP comparator study. We decided it was not appropriate to include the SSPR for celiac disease from Ref. [7] in a pooled SSPR estimate because it was a UK study, and prevalence of celiac disease may differ by region, and also because a UK GP prevalence comparator was used. Using the three remaining studies that provided data on celiac disease prevalence in POTS patients, a pooled estimate of the SSPR for celiac disease of 2.75 with 95% confidence interval (1.06–4.40) was obtained.

Pooled 'exploratory' SSPRs (exploratory because [12] was used as the GP comparator) for 'any AD' and the other individual ADs based on [6,3] were as follows (reported as condition SSPR (95% confidence interval)): 'Any AD', 2.55 (2.25–3.50); rheumatoid arthritis, 2.18 (1.48–3.36); Hashimoto's thyroiditis, 4.23 (3.74–6.47); SLE, 39.03 (26.84–62.47); Sjögren's syndrome 112.09 (93.32–135.20).

Only one measurement of the prevalence of antiphospholipid syndrome in POTS patients was available (from Ref. [6], and an exploratory SSPR of 168.80 (61.85–374.10) was calculated using [12] as GP comparator.

3.6. Heterogeneity across studies

This was assessed using Forest plots which are shown in Figs. S1–S6 in the supplementary material. For any AD, Hashimoto's thyroiditis, Sjögren's syndrome, rheumatoid arthritis and SLE, since the 95% confidence intervals for the log of SSPR of the two studies by Refs. [6,3] overlapped, there was no heterogeneity between these studies for the stated diseases. For celiac disease, there was no heterogeneity across studies by Refs. [6,3,17] while [7] differed from Refs. [3,17] but not from Ref. [6]. To summarise, for all diseases analysed except for celiac disease, there was no heterogeneity in log of SSPR across the studies. There was heterogeneity in log of SSPR

Table 3
Calculated standardised prevalence ratios for various ADs in people with POTS.

Condition	Study	GP estimate for comparator	No. of observed cases (per 100,000)	No. of expected cases (per 100,000)	Standardised sex-adjusted prevalence ratio	95% Confidence Interval
Any autoimmune disease	[6]	[12]	20 (20,000)	6.1 (6,067)	3.30	2.07–5.00
	[3]	[12]	616 (15,662)	243 (6,178)	2.54	2.34–2.74
	Pooled estimate	–	–	–	2.55	2.25–3.50
Hashimoto's thyroiditis	[6]	[12]	11 (11,000)	1.4 (1,359)	8.09	4.26–14.06
	[3]	[12]	228 (5,797)	55 (1,402)	4.14	3.63–4.70
	Pooled estimate	–	–	–	4.23	3.74–6.47
Celiac disease	[6]	[20]	3 (3,000)	1.2 (1,185)	2.53	0.64–6.89
	[3]	[20]	133 (3,382)	47 (1,193)	2.84	2.38–3.35
	[7]	[21]	4 (4,000)	0.3 (314)	12.73	4.05–30.71
	[17]	[20]	7 (2,108)	3.91 (1,178)	1.79	0.78–3.54
	Pooled estimate (excluding [7]	N/A	–	–	2.75	1.06–4.40
Sjögren's syndrome	[6]	[12]	2 (2,000)	0.024 (24)	81.66	13.69–269.80
	[3]	[12]	112 (2,848)	1 (25)	112.82	93.32–135.20
	Pooled estimate	N/A	–	–	112.09	93.32–135.20
Rheumatoid Arthritis	[6]	[12]	4 (4,000)	1.20 (1,199)	3.34	1.06–8.05
	[3]	[12]	93 (2,365)	48 (1,224)	1.93	1.57–2.36
	Pooled estimate	N/A	–	–	2.18	1.48–3.36
SLE	[6]	[12]	2 (2,000)	0.051 (51)	38.97	6.53–128.70
	[3]	[12]	81 (2,059)	2.1 (53)	39.03	31.20–48.26
	Pooled estimate	N/A	–	–	39.03	26.84–62.47
Antiphospho-lipid syndrome	[6]	[12]	5 (5,000)	0.030 (30)	168.80	61.85–374.10

across the studies by Refs. [7,3,17].

4. Discussion

This systematic review found only four published studies in English which reported on the prevalence of one or more ADs in cohorts of at least 100 POTS patients in the published literature at 19th July 2020, with two of the four studies only mentioning the prevalence of one AD (celiac disease in both cases) as an aside.

Three of the studies were retrospective chart reviews, with two of these being small (100 patients) while the fourth was an online survey almost 4000 POTS patients, but patients in that study self-reported both their POTS and AD physician diagnoses. None of the studies screened prospectively for ADs.

All four studies were assessed as being at risk of bias in various ways using a validated risk of bias instrument [13] and we judged all the studies to have an overall (summary) high risk of bias, principally of under-reporting the presence of ADs, because of the lack of prospective AD screening.

These findings highlight a need for more targeted research into the prevalence of ADs in POTS patients.

We used this limited data, in conjunction with GP prevalence studies, to calculate SSPRs for celiac disease and 'exploratory' SSPRs for 'any AD' and other ADs in POTS patients for each of the four included studies.

A pooled SSPR of 2.75 with 95% confidence interval (CI) of (1.06–4.40) was calculated for celiac disease in POTS patients using the three US studies available: [6,3]; and [17] and a gold standard GP comparator [20]. This suggests that, in the US, celiac disease may be nearly three times more prevalent in POTS patients than in the GP.

The only UK study in the analysis [7] provided data on prevalence of celiac disease in 100 POTS patients. Using [21] as the GP comparator (which provides a point prevalence of celiac disease in 2011 in the Yorkshire and Humber region from the UK's Clinical Practice Research Datalink) gave an SSPR of 12.73 with 95% CI (4.05–30.71). This SSPR is much higher than that seen in the three US studies, with the discrepancy largely due to the UK GP prevalence for celiac disease being only about a quarter that reported for the US [20].

'Exploratory' pooled SSPRs were calculated for 'any AD', rheumatoid arthritis, Hashimoto's thyroiditis, SLE and Sjögren's syndrome using data from two studies: [6,3]. The SSPRs ranged in magnitude from 2.18 95% CI (1.48–3.36) for rheumatoid arthritis to an SSPR of 112.09 95% CI (93.32–135.20) for Sjögren's syndrome. It is perhaps not surprising that Sjogren's syndrome, a common cause of autonomic neuropathy, appears to be more prevalent in POTS, an autonomic nervous system disorder, than in the general population.

The reliability of the SSPRs is reduced by the fact that there was no prospective screening for autoimmunity in any of the four included studies.

The SSPR reliability also depends on the reliability of the GP comparator used. For celiac disease we were able to find a US comparator that used NHANES data 20. The NHANES prevalence was based on serological measurements of tissue transglutaminase and endomysial IgA antibodies, which are tests used in the diagnosis of this AD (although biopsy is required for definitive diagnosis). We considered this NHANES data to be gold standard in terms of being representative of the US GP levels of these antibodies. Hence, the pooled SSPR for the prevalence of celiac disease in POTS patients of 2.75 (1.06–4.40) is, we feel, as reliable as it can be, given that only three US POTS studies providing AD prevalence data were available for the calculation.

All the other SSPRs calculated herein are considerably less reliable and at high risk of bias primarily because no gold-standard data was found that could be used as a GP comparator. Although studies were found reporting GP prevalence, in contrast to Ref. [20]; they did not prospectively screen for ADs and hence they may under-report the level of ADs in the GP, leading to inflated SSPRs in this study.

In searching the literature for GP comparators giving the US prevalence of various ADs we were surprised at the dearth of studies and by the wide variation in prevalence in the few studies we found (Supplementary Table 1). Perhaps this should not be so surprising given the rarity of many ADs and the fact that they do not appear to be routinely assessed in NHANES data collection. This begs the question of why ADs are not routinely included in NHANES?

Faced with no gold standard prevalence studies for 'any AD' or the other five ADs we used [12] as the GP comparator for these SSPRs. Advantages of [12] were that it was, to the best of our knowledge, the most recent comprehensive review of all ADs; it was carried out by immunologists; and for each AD, it gave an estimate of the percentage of patients that are female which is important since most POTS patients are women. Using the same study as the source of all our GP prevalence data also provided a level of consistency and facilitated a comparison of the relative prevalence of the various ADs in POTS.

However, there were notable drawbacks in using [12] as the GP comparator. For 'all ADs', Sjögren's syndrome, SLE and anti-phospholipid syndrome [12]'s GP prevalence was the lowest of all the studies found in the literature (Supplementary Table 1). Hence it is possible that the very high SSPRs seen for Sjögren's syndrome (112.09 (93.32–135.20)), SLE (39.03 (26.84–62.47)) and anti-phospholipid syndrome (168.80 (61.85–374.10)) are at least in part due to low GP prevalence figures in Ref. [12]. Finally, although we used [12] for GP prevalence to provide consistency, their review drew on different studies of varying quality from throughout the literature to produce their prevalence estimates for each AD (details in Supplementary Table 1). Of note, their estimate for 'any AD' appears to have been calculated by summing the prevalence for all individual ADs.

One approach might have been simply not to calculate SSPRs for any AD and the five ADs other than celiac disease. However, we felt that calculating 'exploratory' SSPRs would generate questions for further research, albeit bearing in mind that such SSPRs were at high risk of bas.

A strength of this study is that it brings together the available evidence (albeit sparse) on comorbid ADs from (to the best of our knowledge) all cohorts of more than 100 POTS patients reported in the English language to 19th July 2020.

A further strength is that we used SSPRs and thus accounted for the predominantly female nature of POTS cohorts, and also for the differences in prevalence by sex of the various ADs examined. For celiac disease, the tendency of POTS patients to be of White ethnicity was accounted for too, by using an ethnicity-specific GP comparator. We believe this is the first study of ADs in POTS patients to make such adjustments.

Prior to this systematic review, to the best of our knowledge, the most comprehensive numerical estimates of the prevalence of comorbid ADs in POTS patients relative to the GP were made by Ref. [6]. She compared the prevalence of several ADs in a cohort of 100 of her patients with POTS to estimates of GP prevalence using odds ratio, concluding that "patients with POTS have a higher prevalence of autoimmune markers and comorbid ADs than the general population". Significant odds ratios greater than 1 with 95% confidence intervals were quoted for Hashimoto's thyroiditis, rheumatoid arthritis and SLE.

However, odds ratio is not used when comparing the odds of a disease in one population to that in another, rather, its use is confined to comparisons within the same population and under restrictive conditions by what is known as prevalence odds ratio [22]. It is also not clear whether [6]'s calculations took account of the predominantly female nature of the POTS sample, as well as the fact that ADs tend to differ in their prevalence by sex.

In [6]'s cohort, diagnoses of the various ADs "were made or confirmed by the patient's specialist, such as endocrinologist, rheumatologist, gastroenterologist or primary care physician". Blitshteyn says that diagnosis of APS was made using Sapporo criteria (but which version is not made clear) and diagnoses of SLE and Sjögren's syndrome were made using "standard diagnostic criteria". She adds that diagnosis of celiac disease was confirmed via small intestine biopsy in all such diagnosed patients, but we do not know what case definition was used for celiac disease or indeed any of the ADs examined. Given that the diagnostic criteria used for the ADs in Ref. [6] are unknown, over or under-diagnosis may have occurred.

With the exception of celiac disease, the GP prevalence estimates used by Ref. [6] as comparators had limitations. Two sources (Lancet [23,24] quoted GP prevalence without justification or reference. Of particular concern, the figure used for antiphospholipid GP prevalence of 4,000 per 100,000 population [23] is much higher than that quoted by three other independent sources of between 22 and 50 per 100,000 population respectively [12,25,26]. It is likely that [6] selected this high value because of her stated aim to be conservative, but on the other hand, the use of this value in preference to other, perhaps more reliable, sources could mean that an increased prevalence of antiphospholipid syndrome in people with POTS was overlooked. Finally, the GP prevalence values [6] used for RA [27] and SLE [28] were quite old, particularly the latter, which was based on data from 1993.

The study by Ref. [7] was an investigation of self-reported gluten sensitivity from a retrospective chart review of 100 consecutive POTS patients being treated at a large hospital outpatient clinic in the UK. The prevalence of celiac disease in these medical records (confirmed by serology and biopsy) in the POTS cohort (4 patients, or 4,000 per 100,000) was compared with data from Ref. [18] which used medical records of 1200 controls taken from five primary care clinics in the same UK county between 1999 and 2001 (12 patients, prevalence 1,000 per 100,000). The authors reported an odds ratio of 4.1. However, once again, the use of odds ratio, rather than a standardised prevalence ratio was inappropriate. Further, the control group, although from the local area, was not ideal, as it had an older median age (46 years in controls vs 27 years in the POTS cohort) and a lower proportion of women (63% vs 84%).

The online survey by Ref. [3]; gave self-reported prevalence of several physician-diagnosed comorbid ADs, but did not compare prevalence in POTS patients with the GP. POTS patients in the study were asked whether a doctor had diagnosed them with any of a list of medical conditions, which included Sjogrens syndrome, "lupus", rheumatoid arthritis, Hashimoto's thyroiditis and celiac disease. No case definitions were given and there was potential for volunteer bias in the study design.

In [17]'s study seven of the patients in the historical review of Mayo clinic POTS patient medical records were noted as having celiac disease, with the diagnostic criteria used not reported. No comparison was made with the general population.

Apart from limitations due to the lack of gold standard GP comparators for all ADs except celiac disease in the US, our analysis has further limitations.

First, Blitshteyn [6] and [7] were small studies with only 100 POTS patients each. In such small cohorts, having one case more or less has a large effect on the prevalence, and hence the antiphospholipid syndrome result, in particular (which is derived solely from Ref. [6], must be treated with caution. However, with the inverse variance method used for calculating pooled results, data from the largest study [3], carries most weight in our pooled analyses for other ADs.

Second, although prevalence ratios were sex-adjusted in our analysis, they were not age-adjusted. The age-profile of POTS patients is younger than the GP and allowing for this would further improve future analyses. Certain ADs might be more prevalent in young people and this may account for part, or all, of the higher prevalence observed in POTS patients.

Third, Blitshteyn (2015) [7], and [17]Tseng were retrospective chart reviews of patient cohorts while [3] was an online survey relying on self-report of both POTS and ADs. Pooling the results of studies carried out using different methodologies is not ideal. However, we felt that [3]'s study added significantly to the data on ADs in POTS and should be included.

None of the studies were longitudinal and we have no information on whether POTS preceded or followed AD diagnoses hence no temporal link can be made in either direction.

The exploratory findings here of a very high prevalence of Sjögren's syndrome, SLE and antiphospholipid syndrome in POTS patients should be tested in a prospective, methodical clinical assessment of ADs in a large cohort of POTS patients versus age/sex matched healthy controls. Since POTS patients represent a population very different from the general population (with a predominance of young women), it is important that comparator groups in POTS studies are age- and sex-matched.

5. Conclusions

Our systematic review identified a dearth of research on the topic, finding only four studies that reported the prevalence of at least

one AD in cohorts ($n \geq 100$) of POTS patients in the English literature to 19th July 2020. Three studies were retrospective chart reviews (two being small cohorts with $n = 100$) and one was an online self-selected online survey of about 4000 patients.

All studies were assessed as being at high risk of bias overall, mainly because none of them screened participants prospectively for ADs. These findings highlight the need for targeted research into the prevalence of ADs in POTS patients.

In what believe is the first study to calculate pooled SSPRs for ADs in POTS patients, our analysis confirms earlier reports that certain ADs may be more prevalent, and possibly markedly more prevalent, in these patients.

We calculated that celiac disease is significantly more prevalent in US POTS patents than in the general population (SSPR 2.75 95% % CI (1.06–4.40)), in an analysis that recognised that POTS patients are predominantly of White ethnicity and used a gold-standard GP comparator.

Our exploratory results suggested that Sjögren's syndrome, SLE and, possibly, antiphospholipid syndrome, may be many-fold more prevalent in POTS patients than the GP. Furthermore, because none of the studies prospectively screened for autoimmune diseases, there is a risk of bias towards under-reporting of these ADs in these patients.

However, our exploratory results are also at high risk of bias due to the dearth of gold standard GP comparators, and since the comparator studies themselves rarely involved prospective screening for ADs, they may under-report the level of ADs in the GP, leading to inflated SSPRs in this study. We also note that our SSPR for antiphospholipid syndrome is based on results from only one small POTS cohort.

We noted a surprising variability in published estimates of US GP prevalence for ADs in the literature, suggesting the need for further and more-comprehensive studies in this field.

Our findings need to be confirmed in a large cohort of POTS patients ($n > 1{,}000$) that is compared with an age and sex-matched cohort from the GP.

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The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e12982.

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