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Tick exposures and alpha-gal syndrome: A systematic review of the evidence

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ABSTRACT

Alpha-gal syndrome (AGS) refers to a delayed allergic reaction to galactose-α-1,3-galactose (α-Gal) that occurs following the consumption of mammalian meat or exposure to other animal-based foods and products. Increasing evidence suggests that bites from certain tick species can lead to AGS through sensitization of a person's α-Gal specific IgE levels. This systematic review aimed to summarize the published evidence on this topic to understand post-tick exposure AGS epidemiology and health outcomes. A structured search for literature in eight bibliographic databases was conducted in January, 2020. Grey literature and verification searches were also performed. The exposure of interest was tick bites, and the outcome of interest was AGS. All primary research study designs were eligible for inclusion. References were screened for relevance, and data extraction and risk-of-bias assessment were conducted on relevant studies by two independent reviewers. Data were descriptively and narratively summarized. Of 1390 references screened, 102 relevant articles (103 unique studies) were identified (published from 2009 to 2020). Most studies (76.7 %) were case report or series. These 79 studies reported on 236 post-tick exposure AGS cases from 20 different countries, mostly the United States (33.5 %), Spain (19.5 %), Sweden (18.6 %), and France (12.7 %). The mean case age was 51.3 (SD = 16.7, range 5–85, n = 229), while 68.1 % were male (n = 226). The most commonly reported symptom was urticaria (71.2 %); 51.7 % of cases reported anaphylaxis. Twenty-one observational studies were reported, mostly (95.2 %) among clinical allergy patients. The proportion of AGS cases that recalled tick bites was highly variable across these studies. Three challenge studies evaluating tick exposures and α-Gal levels in α-Gal deficient mice were identified. The existing evidence suggests tick bites lead to α-Gal-specific IgE sensitization, which can cause AGS, but further research is needed to clarify if AGS is only attributable to certain tick species and whether other vectors may trigger AGS. Additional research is needed on risk factors for AGS development, evaluation of diagnostic immunoassays, and the epidemiology and distribution of AGS in different populations. Climate change will likely lead to future cases of AGS in new regions worldwide due to the predicted alteration of suitable tick habitats.

1. Introduction

Alpha-gal syndrome (AGS), commonly referred to as mammalian meat allergy, is characterised by an allergic reaction to galactose-α-1,3-galactose (α-Gal) (Chung et al., 2008; Commins et al., 2009; Hilger et al., 2019; O'Neil et al., 2007). The α-Gal carbohydrate is present in most mammals, including livestock, but absent in humans and some primates (Hilger et al., 2019). Individuals with AGS develop hypersensitivities to α-Gal; clinically this presents as delayed allergic reactions to mammalian meat, and sometimes other products derived from mammals that contain α-Gal (e.g. dairy products, gelatin-containing colloids, and pharmaceuticals) (Commins, 2020; Commins et al., 2009; Fischer et al., 2014; Hilger et al., 2019; Platts-Mills et al., 2020a, 2020b; Wilson et al., 2019). In contrast to traditional food allergies, the presentation of allergic reactions in AGS is delayed, and typically occurs within several hours after the consumption of mammalian meat or other animal-based food products (Commins et al., 2014; Fischer et al., 2014; Hilger et al., 2019; Platts-Mills et al., 2020a; Wilson et al., 2019). Symptoms of AGS vary, ranging from severe anaphylaxis to angioedema, urticaria, pruritus, or gastrointestinal complications (e.g. abdominal pain) – the latter may occur with or without skin reactions (Commins, 2020; Commins et al., 2014; Fischer et al., 2014; Platts-Mills et al., 2020a; Wilson et al.,

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2019).

AGS was first recognized through the identification of specific IgE antibodies targeting α-Gal among patients experiencing allergic reactions to the cancer treatment drug cetuximab (Chung et al., 2008; Hilger et al., 2019; O'Neil et al., 2007; Platts-Mills et al., 2020b, 2020a). IgE antibodies targeting α-Gal were then identified among individuals with hypersensitivities to mammalian meat and other meat by-products (Commins et al., 2009; Fischer et al., 2014). In 2009, Australian researchers published the first report correlating tick bite exposure and AGS, then United States (U.S.) researchers established the same link by examining the overlap between the location of cetuximab reactions and cases of Rocky Mountain spotted fever, a disease transmitted by the lone star tick *Amblyomma americanum* (Commins et al., 2011; Hilger et al., 2019; Platts-Mills et al., 2020a; Van Nunen et al., 2009). AGS has since been documented in various regions worldwide, including the U.S., Europe, Australia, Japan, and South Africa (Chinuki et al., 2016; Fischer et al., 2017, 2014; Hamsten et al., 2013; Mabelane et al., 2018; Platts-Mills et al., 2020a; Van Nunen et al., 2009).

In the U.S., tick bites from *A. americanum* are believed to be the primary cause of AGS (Commins et al., 2011; Platts-Mills et al., 2020a). However, the presence of case clusters in regions outside of the current range of this tick suggests that other tick species or vectors (e.g. chiggers) might also contribute to α-Gal sensitization (Crispell et al., 2019; Platts-Mills et al., 2020a; Stoltz et al., 2019; Wilson et al., 2020). Globally, other species of ticks implicated in causing AGS include *Ixodes ricinus*, *Ixodes holocyclus*, and *Haemaphysalis longicornis* (Chinuki et al., 2016; Fischer et al., 2017; Platts-Mills et al., 2020a; Van Nunen et al., 2009). The mechanism by which ticks induce α-Gal sensitization in humans is not fully understood, but likely relates to the presence of α-Gal antigen in the saliva of certain tick species (Crispell et al., 2019; Platts-Mills et al., 2020a). Furthermore, the source of α-Gal in ticks is uncertain; hypotheses include the ability of certain ticks to intrinsically synthesize α-Gal, the presence of residual amounts of α-Gal in tick saliva from prior blood meals, and/or the production of α-Gal in tick saliva by microbial symbionts (Fischer et al., 2020b; Platts-Mills et al., 2020a).

The geographic distribution of tick vectors, including *A. americanum*, is expected to be altered by climate change, with northward expansion across the U.S. and into Canada (Nelder et al., 2019; Sagurova et al., 2019; Stafford III et al., 2017). Further, climate change may lead to an accelerated tick life cycle, increasing their abundance and seasonal questing activity (Bouchard et al., 2019; Ogden and Lindsay, 2016). Therefore, future cases of AGS could be detected in areas of the U.S. and in the southern regions of Canada where *A. americanum* is currently not established. While recent reviews have summarized prior research on AGS (Hilger et al., 2019; Platts-Mills et al., 2020a, 2020b), none used a structured, knowledge synthesis methodology or focused specifically on AGS epidemiology and health outcomes. Therefore, we conducted a systematic review (SR) of the existing evidence on post-tick exposure AGS epidemiology and health outcomes as part of the Public Health Agency of Canada's ongoing initiative to evaluate the impacts of climate change on vector-borne diseases and human health. Results from this SR can support future research needs and planning for AGS prevention and management across Canada, the U.S., and other countries worldwide.

2. Materials and methods

2.1. Review question and eligibility criteria

This SR adheres to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines and was conducted following a protocol developed *a priori* (Supplementary material) (Moher et al., 2009). The primary research question was: "what is the existing evidence on developing AGS following tick bite exposures in human populations and humanized animal models?" Specific sub-questions of interest included: 1) what is the evidence linking tick exposures to the development of AGS? and 2) what evidence has been reported on AGS epidemiology, adverse outcomes, time to AGS symptom presentation, and long-term sensitizations to α-Gal?

Our exposure of interest was tick bites, including self-reported, clinically diagnosed, and experimental tick or tick substrate exposures. Our outcome of interest was post-tick exposure AGS epidemiology, symptoms, adverse outcomes, time to symptom development, long-term sensitization, and human risk factors. We defined AGS as the delayed clinical presentation of hypersensitivity reactions (e.g. anaphylaxis, skin reactions, gastrointestinal symptoms) after the consumption of mammalian meat or animal by-products, or immediately after injection of pharmaceutical products containing α-Gal (e.g. cetuximab), and confirmed through the identification of anti-α-Gal IgE antibodies in serum, a skin prick test, and/or clinician diagnosis (Chung et al., 2008; Commins et al., 2014). Our population of interest included humans, as well as humanized animal models (e.g. experimental studies of mice deficient in α-Gal). All primary research study designs were considered eligible, including observational studies, experimental studies, case reports and series, and surveillance reports. Articles published in any language were included, with non-English articles translated using Google translate.

2.2. Search strategy

A comprehensive search strategy was developed and pre-tested in an iterative process by an experienced information specialist in consultation with the review authors. Searches were conducted in the following eight bibliographic databases from 17 to 21 January, 2020: Ovid MEDLINE, Embase, CINAHL, PsycINFO, CENTRAL, Global Health, ProQuest Dissertation and Theses, Scopus, and Cochrane Database of Systematic Reviews. The search algorithm consisted of a combination of AGS and meat-allergy terms combined with tick-related terms (see Supplementary material for details). No publication date restrictions were applied to the searches.

A complementary search for grey literature and reports of ongoing studies was conducted in January 2020 using Google and the specialized electronic database OpenGrey. These searches used combinations of keywords and phrases to mimic the more sophisticated algorithms used for bibliographic databases. For practical and logistical reasons, only the first 100 relevant hits were searched. Additionally, we conducted targeted searches in 11 other health and government agency websites and databases, including ProMED-mail and MetaLib (see the Supplementary material protocol for further details). Reference lists of 19 relevant review articles were scanned to identify additional potentially relevant literature missed by our electronic searches.

2.3. Study selection

References identified through the searches were imported to EndNote X7 (Clarivate Analytics, Philadelphia, PA) for duplicate removal. Unique references were then imported to the web-based SR program DistillerSR (Evidence Partners, Ottawa, ON) to facilitate review management and progress. Two independent reviewers screened the title and abstract of each unique reference for eligibility using a structured screening form developed *a priori*. The form consisted of one yes/no question to determine relevance to the SR question and eligibility criteria. Prior to implementation, the form was pre-tested by five reviewers on a random sample of 50 references. No reviewing conflicts were identified in the pre-test.

2.4. Relevance confirmation and data extraction

The full-texts of included references were obtained and assessed using a second-level screening form. This form contained three questions to determine the article type, research topic, and population investigated to confirm study eligibility. Key study characteristics and data were then extracted from relevant articles using another structured, pre-

specified form. Extracted characteristics included publication details (e.g. year, language), study design, sample location and period, population details (e.g. type, demographics), tick exposure details (e.g. species, method of measurement), sources of α-Gal, AGS testing and diagnostic methods, AGS symptoms and adverse outcomes, human risk factors for AGS, long-term sensitizations, and time to AGS symptom presentation. Both forms were pre-tested by five reviewers on a sample of 10 articles. Pre-testing results were discussed and the forms were slightly modified before implementation to improve clarity and consistency of interpretation. Two reviewers independently extracted all data. Conflicts between reviewers were resolved through discussion and consensus. All SR forms are available in the protocol (Supplementary material).

2.5. Risk-of-bias assessment

Our SR protocol intention was to assess all relevant articles for risk of bias using a preliminary version of the "Risk Of Bias In Non-randomized Studies - of Exposures" (ROBINS-E) tool (University of Bristol, 2020). However, after pre-testing seven articles with this tool, we determined that it was not suitable for use in this SR given the variety of study designs included. We instead used validated critical appraisal tools from the Joanna Briggs Institute, with different tools applied depending on the specific study design (Moola et al., 2020; Munn et al., 2014). We included tools for seven different study designs: cross-sectional; case--control; cohort; prevalence; case reports; case series; and non-randomized controlled trials (Moola et al., 2020). The tools included 7–12 questions each, assessing various study-specific risk-of-bias criteria (Moola et al., 2020). While the specific questions differed by study design, in general they focused on determining possible selection bias (e.g. inappropriate or non-representative sampling frame), information bias (e.g. misclassification or inadequate measurement of variables), confounding bias (e.g. inadequate consideration or control of possible confounding variables), and/or reporting bias (e.g. insufficient reporting of key details to allow possible replication and informed inferences) (Moola et al., 2020; Murad et al., 2018). One minor modification was made to the tools: the overall appraisal responses were changed from 'include', 'exclude', and 'seek further info' to 'high', 'low', and 'unclear' risk of bias, to conform with the Cochrane Collaboration approach (Higgins et al., 2020). Each tool was pre-tested on one article (n = 7 total) by four independent reviewers. Results were compared and discussed to ensure consistent interpretation among reviewers. Reviewing of remaining articles was conducted by two independent reviewers, with conflicts resolved through discussion and consensus.

2.6. Data analysis

Given the variability in study designs and outcomes reported, we did not perform a meta-analysis; instead, we conducted a descriptive and narrative synthesis of study results (Mays et al., 2005; Moola et al., 2020). For case reports and series, we extracted individual case data and conducted a descriptive analysis (e.g. frequency tabulations) of case characteristics. In these studies, the reported time from consumption of meat or other animal-based foods to onset of AGS symptoms was frequently reported as a range. Therefore, to provide an informative summary of these data, ranges were split into lower, median, and higher end values, and the mean and standard deviation (SD) of each value was calculated. For cases that provided only a single time-to-onset value (e.g. 4 h after consumption), the value was placed in each of the lower, median, and higher end categories. For all other study designs, we calculated frequency tabulations of key study characteristics and summarized individual study-level data in a tabular format.

3. Results

3.1. Study characteristics

A total of 1390 references were screened for eligibility, of which 102 relevant articles, reporting on 103 unique studies, were identified (Fig. 1). Grey literature searching identified 15 unique references, with all others identified from bibliographic database searches. The characteristics of the relevant articles and studies are shown in Table 1. More than one-third (36.2 %) of articles were conference proceeding abstracts or papers, and 95.1 % of articles were published in English. Publication dates ranged from 2009 to 2020 (median 2016), with an increasing trend over time. Among the 103 unique studies, 76.7 % were case reports or series. The studies were primarily conducted in the U.S. (40.8 %) and Europe (40.8 %). Ninety-seven percent of the studies (n = 100) focused on humans, with three investigating humanized animal models. Twenty-eight percent of studies (n = 29) reported their dates of data collection. Spreadsheets of all extracted study characteristics and data, including a list of excluded articles, are provided as Supplementary material.

3.2. Risk-of-bias assessment

A summary of the overall risk-of-bias assessment ratings for each of the study designs is shown in Table 2, and summary ratings for individual risk-of-bias criteria are shown for the three most common study designs in Table 3 (case reports, case series, and prevalence surveys). Complete risk-of-bias results and criteria for each individual study, stratified by study design, are reported as Supplementary material. Eighty-four percent of case reports and 86.4 % of case series were assessed to be at high risk of bias. Of 57 case reports, 29.8 % clearly described the diagnostic tests or assessment methods used, and 42.1 % clearly described the patient's post-intervention or follow-up clinical status. Of 22 case series studies, 90.9 % did not clearly indicate if participant inclusion was consecutive, 100 % did not indicate if participant inclusion was complete, and 27.3 % clearly reported demographic information about the presenting site or clinic. All prevalence surveys were rated as high (53.3 %) or unclear (46.7 %) overall risk of bias, with studies providing incomplete or unclear information for several criteria. All three experimental studies were assessed as unclear risk of bias, while the other observational studies had variable risk-of-bias ratings.

3.3. Case reports and series

Summary information was reported for 236 unique post-tick exposure AGS cases in 79 studies (Table 4). Twenty-two (27.8 %) studies reported data for more than one case (median 3.5, range 2–39). Cases were reported from 20 different countries, most commonly the U.S. (33.5 %), Spain (19.5 %), Sweden (18.6 %), and France (12.7 %). The 79 U.S. cases were reported across 20 states, most frequently Virginia (53.2 %). The mean age, among 229 cases with age information available, was 51.3 (SD = 16.7, range 5–85). Eleven cases (4.8 %) occurred among those aged 19 years or younger (Fig. 2). Among 226 cases with gender information available, 68.1 % were male. For the 77 cases where ethnicity information was reported, all were white. The date of AGS symptom onset was reported for 33.1 % of cases (n = 78), which ranged from less than one to several years prior to the study publication date.

Co-morbidities (e.g. asthma, cardiovascular disease, hypertension) were reported among 9.7 % of cases. The most commonly reported possible risk factor for post-tick exposure AGS was having a non-B blood type (37.7 %). Ninety-eight percent of cases were exposed to α-Gal via the consumption of meat or meat by-products; most commonly beef (41.5 %) and pork (39.4 %). Tick exposure was identified for all but one case via patient self-reporting, with a specific tick species identified in 3.8 % of cases. Among 11.0 % of cases that remembered the approximate time interval between their last tick bite and onset of AGS symptoms,

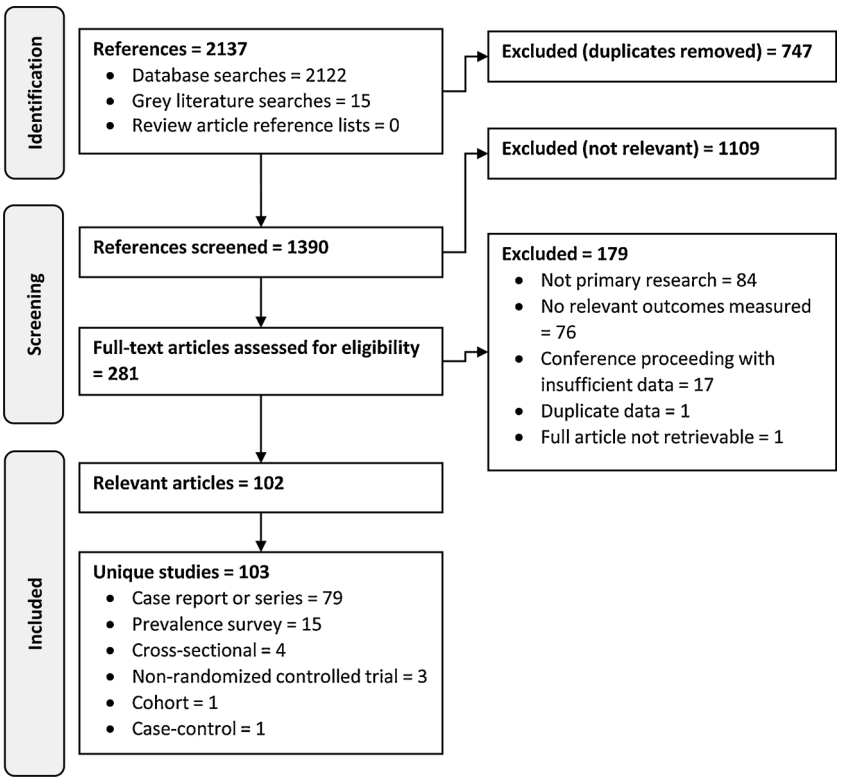

Fig. 1. Systematic review flow diagram.

timeframes ranged from weeks to years.

Among 236 cases reported in 79 studies, symptoms most commonly involved skin reactions (74.6 %), primarily urticaria (71.2 %), while 51.7 % of cases reported anaphylaxis (Table 5). One or more gastrointestinal symptoms were reported by 30.1 % of cases, while 17.4 % reported respiratory symptoms and 15.3 % reported various other symptoms. Twenty cases (8.5 %) reported having to visit an emergency department as a result of severe clinical symptom presentation; no deaths were reported. Of the 232 cases that experienced AGS symptoms from consuming meat or other animal-based foods, 83.2 % reported their post-consumption time to symptom development. The mean time to development of symptoms was 4.5 h (SD = 1.4); mean lower range of 3.5 h (SD = 1.7, range = 10 min to 10 h) and mean higher range of 5.8 h (SD = 2.4, range = 1–12 h). Among the six cases that reported a time to onset of AGS symptoms from injection of a pharmaceutical product (e.g. intravenous cetuximab, vaccine, antivenom), symptoms occurred rapidly within 2–15 min. The most commonly reported methods of AGS diagnosis were clinician diagnosis (100 %), serum IgE test (99.6 %), and a skin prick test (53.8 %). The most commonly specified IgE test was the ImmunoCAP assay (68.2 %). Among studies that reported a cut-point to determine a positive α-Gal specific IgE test, 47.7 % used $\geq$0.35 kU_A/L and 3.1 % used $\geq$0.10 kU_A/L. De-sensitization to α-Gal through the consumption of small amounts of meat or animal-based foods was reported among seven (3.0 %) cases.

3.4. Observational studies

Summary characteristics of 21 observational studies of post-tick exposure AGS are reported in Table 6, including 15 prevalence surveys, four cross-sectional, one cohort, and one case-control study. Individual study-specific characteristics are reported in Table 7. The population source in these 95.2 % of these studies was clinical allergy patients. Most studies reported the age (81.0 %) and gender (76.2 %) characteristics of their population, but only three (14.3 %) reported on participant ethnicity. The percentage of female participants within specific study samples ranged from 0 to 72 %. Mean and median ages varied widely, from 12 to 66. Ninety-five percent of studies reported α-Gal exposure via the consumption of meat or meat by-products (e.g. foods containing gelatin). Only two (9.5 %) studies reported the likely tick species of exposure, with three (14.3 %) studies reporting information on the time since last tick exposure and AGS symptom development. These times ranged from one week to two years. Similarly, the proportion of AGS cases that recalled tick bites was highly variable across studies. All studies confirmed tick bite exposures through patient self-reporting.

AGS symptoms were reported for participants in 85.7 % of studies. Among these 18 studies, 88.9 % reported that patients experienced skin reactions, most commonly urticaria (83.3 %). Anaphylaxis was reported by 77.8 % of studies, and one or more gastrointestinal (55.6 %) or various other symptoms (55.6 %) were also commonly reported. Two studies reported that one or more patients experienced emergency department visits due to their reactions. Of the 10 studies that reported approximate times from α-Gal exposure to AGS symptoms, these tended to occur within 2–6 h, though reported times ranged from <30 min to 24 h. Methods used to diagnose AGS included serum IgE tests (100 % of studies), most commonly the ImmunoCAP assay (76.2 %), and clinician diagnosis (90.5 %). For studies that used the ImmunoCAP assay, cut-points to determine a positive α-Gal specific IgE test varied between $\geq$0.35 and $\geq$0.10 kU_A/L. Three studies reported on the diagnostic accuracy of the applied test and one reported on α-Gal de-sensitization in AGS patients during follow-up.

3.5. Experimental studies

Three non-randomized controlled trials investigating AGS in mice were identified (Table 8). All three studies investigated α-Gal specific IgE responses in mice exposed to *A. americanum* tick saliva extract vs. saline as a control, then evaluated immune response outcomes following oral challenges with α-Gal-containing beef thyroglobulin or pork meat. All three studies found that tick exposure led to elevated α-Gal specific

Table 1
Summary characteristics of 102 relevant articles and 103 unique studies that investigated alpha-gal syndrome following tick bite exposures in human populations and humanized animal models.

Article and study characteristics	No. of articles or studies	% of articles or studies
Document type (n = 102 articles):		
Journal article—research paper	50	49.0
Conference proceeding abstract or article	37	36.2
Journal article—letter to the editor or expert opinion with primary research data	15	14.7
Publication language (n = 102 articles):		
English	97	95.1
French	3	2.9
Spanish	1	1.0
German	1	1.0
Study design (n = 103 studies):		
Case report or series	79	76.7
Prevalence survey	15	14.6
Cross-sectional	4	3.9
Non-randomized controlled trial	3	2.9
Cohort	1	1.0
Case-control	1	1.0
Study location (n = 103 studies):		
U.S.	42	40.8
Europe:	42	40.8
France	11	10.7
Germany	7	6.8
Spain	7	6.8
Sweden	4	3.9
Italy	2	1.9
Norway	2	1.9
United Kingdom	2	1.9
Other[a]	6	5.8
Australia	6	5.8
Japan	5	4.9
South Africa	2	1.9
Turkey	2	1.9
Other[b]	3	2.9
Not reported	3	2.9
Population assessed (n = 103 studies):		
Humans	100	97.1
Humanized animal models	3	2.9
Data collection dates reported (n = 103 studies):		
Yes	29	28.2
No	74	71.8

[a] Other European countries include n = 1 for Austria, Belgium, Czech Republic, Denmark, Romania, and Switzerland.
[b] Other countries include n = 1 for Brazil, Canada, and China.

Table 2
Overall risk-of-bias ratings for 103 relevant studies that investigated alpha-gal syndrome following tick bite exposures in human populations and humanized animal models.

Study design	No. of studies	Overall risk-of-bias rating: n (%)		
		High	Unclear	Low
Case report	57	48 (84.2)	1 (1.8)	8 (14.0)
Case series	22	19 (86.4)	3 (13.6)	0 (0)
Prevalence survey	15	8 (53.3)	7 (46.7)	0 (0)
Cross-sectional	4	1 (25.0)	1 (25.0)	2 (50.0)
Non-randomized controlled trial	3	0 (0)	3 (100)	0 (0)
Cohort	1	1 (100)	0 (0)	0 (0)
Case-control	1	1 (100)	0 (0)	0 (0)

IgE levels in treated vs. control mice. The two studies that measured mast cell protease levels post-challenge found increased levels in challenged vs. control mice. All three studies measured post-challenge body temperature changes, with two finding a temperature reduction in challenged vs. control mice.

Table 3
Summary risk-of-bias criteria for 57 case reports, 22 case series, and 15 prevalence studies that investigated alpha-gal syndrome following tick bite exposures in human populations.

Study design and criteria	Risk-of-bias response: n (%)		
	Yes	No	Unclear
Case reports:			
Were patient's demographic characteristics clearly described?	49 (86.0)	8 (14.0)	0 (0)
Was the patient's history clearly described and presented as a timeline?	36 (63.2)	20 (35.1)	1 (1.8)
Was the current clinical condition of the patient on presentation clearly described?	46 (80.7)	11 (19.3)	0 (0)
Were diagnostic tests or assessment methods and the results clearly described?	17 (29.8)	32 (56.1)	8 (14.0)
Was the intervention(s) or treatment procedure (s) clearly described?	34 (59.6)	19 (33.3)	4 (7.0)
Was the post-intervention clinical condition clearly described?	24 (42.1)	28 (49.1)	5 (8.8)
Does the case report provide takeaway lessons?	49 (86.0)	8 (14.0)	0 (0)
Case series:			
Were there clear criteria for inclusion in the case series?	13 (59.1)	8 (36.4)	1 (4.5)
Was the condition measured in a standard, reliable way for all participants?	8 (36.4)	1 (4.5)	13 (59.1)
Were valid methods used for identification of the condition for all participants?	11 (50.0)	0 (0)	11 (50.0)
Did the case series have consecutive inclusion of participants?	2 (9.1)	1 (4.5)	19 (86.4)
Did the case series have complete inclusion of participants?	0 (0)	0 (0)	22 (100)
Was there clear reporting of the demographics of the participants?	18 (81.8)	4 (18.2)	0 (0)
Was there clear reporting of clinical information of the participants?	19 (86.4)	3 (13.6)	0 (0)
Were the outcomes or follow up results of cases clearly reported?	8 (36.4)	12 (54.5)	2 (9.1)
Was there clear reporting of the presenting site (s)/clinic(s) demographic information?	6 (27.3)	16 (72.7)	0 (0)
Was statistical analysis appropriate?[a]	3 (42.9)	0 (0)	4 (57.1)
Prevalence surveys:			
Was the sample frame appropriate to address the target population?	8 (53.3)	0 (0)	7 (46.7)
Were study participants sampled in an appropriate way?	3 (20.0)	1 (6.7)	11 (73.3)
Was the sample size adequate?	0 (0)	0 (0)	15 (100)
Were the study subjects and the setting described in detail?	7 (46.7)	7 (46.7)	1 (6.7)
Was the data analysis conducted with sufficient coverage of the identified sample?	3 (20.0)	0 (0)	12 (80.0)
Were valid methods used for the identification of the condition?	8 (53.3)	1 (6.7)	6 (40.0)
Was the condition measured in a standard, reliable way for all participants?	7 (46.7)	1 (6.7)	7 (46.7)
Was there appropriate statistical analysis?[b]	7 (58.3)	0 (0)	5 (41.7)
Was the response rate adequate, and if not, was the low response rate managed appropriately?[c]	0 (0)	1 (12.5)	7 (87.5)

[a] This question was not applicable for 15 studies (statistical analysis not conducted); percentages reflect the number of studies to which the question applied.
[b] This question was not applicable for three studies (statistical analysis not conducted); percentages reflect the number of studies to which the question applied.
[c] This question was not applicable for seven studies (participants selected from a secondary data source); percentages reflect the number of studies to which the question applied.

Table 4
Demographic and exposure characteristics of 236 post-tick exposure alpha-gal syndrome cases reported in 79 case report and series studies.

Case characteristics	No. of cases	% of cases
Country of occurrence:		
U.S.	79	33.5
Spain	46	19.5
Sweden	44	18.6
France	30	12.7
Germany	6	2.5
Japan	6	2.5
Belgium	4	1.7
Australia	4	1.7
Norway	2	0.8
South Africa	2	0.8
Turkey	2	0.8
United Kingdom	2	0.8
Other[a]	9	3.8
U.S. states of occurrence (n = 79)[b]:		
Virginia	42	53.2
Missouri	9	11.4
New Jersey	4	5.1
Tennessee	3	3.8
Alabama	2	2.5
Arkansas	2	2.5
Kansas	2	2.5
New York	2	2.5
North Carolina	2	2.5
Other[c]	11	13.9
Gender (n = 226)[d]:		
Male	154	68.1
Female	72	31.9
Date of onset reported:		
Yes	78	33.1
No	158	66.9
Co-morbidities reported:		
Yes	23	9.7
No	213	90.3
Possible risk factors reported[e]:		
Non-B blood type	89	37.7
Outdoor recreational activities	29	12.3
Medication use	9	3.8
Alcohol use	8	3.4
Outdoor occupation	8	3.4
Pet ownership	7	3.0
Geographic location (e.g. forested area)	6	2.5
Travel	1	0.4
None reported	108	45.8
α-Gal exposure methods[e]:		
Consumption of meat or animal by-products:	231	97.9
Beef	98	41.5
Pork	93	39.4
Lamb	51	21.6
Game meat	8	3.4
Other animal meat (e.g. goat, ox)	4	1.7
Poultry	3	1.3
Gelatin-containing product	3	1.3
Type of meat not reported	110	46.6
Consumption of dairy products	16	6.8
Pharmaceutical product	14	5.9
Animal-based heart valve replacement	2	0.8
Other[f]	2	0.8
Method of determining tick exposure:		
Patient self-report	235	99.6
Clinician diagnosis	1	0.4
Tick species of exposure:		
Amblyomma americanum	5	2.1
Haemaphysalis longicornis	2	0.8
Ixodes ricinus	1	0.4
Ixodes australiensis	1	0.4
Not confirmed or reported	227	96.2
Approximate time from last recalled tick exposure to AGS symptoms:		
One to three weeks	8	3.4
One to several months	9	3.8
One to several years	9	3.8
Not reported	210	89.0

[a] One case reported in each of Austria, Brazil, China, Czech Republic, Denmark, Italy, Romania, Switzerland, and an unclear location in either France or Luxembourg.
[b] Percentages were tabulated out of the number of cases reported in the U.S. (n = 79).
[c] One case reported in each of California, Connecticut, Florida, Kentucky, Louisiana, New Hampshire, Ohio, Oklahoma, South Carolina, West Virginia, and an unreported location.
[d] Percentages were tabulated out of the number of cases that reported a gender (n = 226).
[e] Multiple selections were possible for these variables, so percentages do not add to 100 %.
[f] One case each reported possible reactions from consuming an egg dish and flounder roe, respectively.

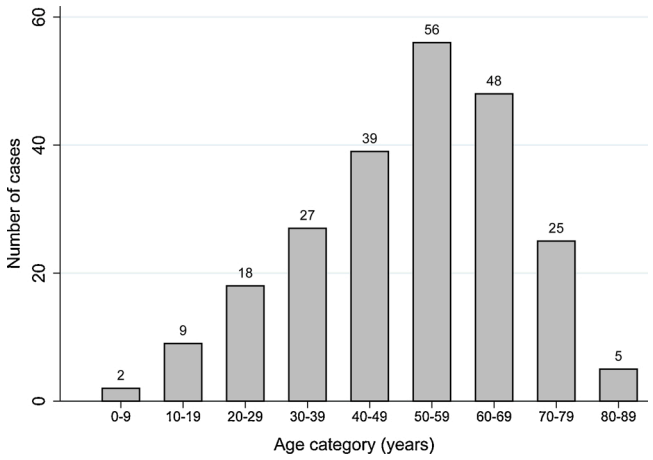

Fig. 2. Age distribution of 229 cases of post-tick exposure alpha-gal syndrome, reported from 2011–2020.

4. Discussion

This SR has identified and summarized a decade of research on post-tick exposure AGS epidemiology and case characteristics. Over one-third of relevant studies were published as conference proceeding abstracts or articles, with an increasing number of publications in recent years, indicating AGS is still an emerging and growing area of research. The vast majority (76.7 %) of relevant studies were case reports and case series. These study designs are likely to be biased toward more severe cases, but can provide valuable insights and aid in the generation of hypotheses about novel and rare diseases, such as AGS, which can be evaluated with additional research employing different study designs (Murad et al., 2018). Unfortunately, we found that most of the case reports and case series included in this SR were missing important reporting details necessary to evaluate their context and utility. Furthermore, the overall risk of bias was high or unclear for most of the other included observational and experimental studies. We encourage primary research authors in this area to follow key reporting guidelines for future studies (e.g. CARE guidelines for case reports, STROBE guidelines for observational studies) to improve the consistency of reporting of studies and to allow readers to fully assess the merits, context, and outcomes of each study (Gagnier et al., 2013; The EQUATOR Network, 2020; von Elm et al., 2007v).

We identified case reports of post-tick exposure AGS in 20 different countries worldwide. In the U.S., cases were mostly reported across the mid-west and eastern states. One case report was identified of a woman who was exposed to ticks in northern California (Arroyo and Tourangeau, 2015), the only known case in the west U.S. coast. Given that various species of ticks worldwide have been linked to inducing AGS, and that *I. scapularis* has been found to express α-Gal, it is possible that other tick species or vectors could also contribute to AGS (Crispell et al.,

Table 5
Symptoms, outcomes, and diagnosis among 236 post-tick exposure alpha-gal syndrome cases reported in 79 case report and series studies.

Case characteristics	No. of cases	% of cases
Reported symptoms[a]:		
Anaphylaxis	122	51.7
Skin reactions:	176	74.6
Urticaria	168	71.2
Angioedema	59	25.0
Pruritus	34	14.4
Erythema	15	6.4
Respiratory symptoms:	41	17.4
Dyspnea	26	11.0
Bronchospasm / wheezing	10	4.2
Chest / throat tightness	8	3.4
Cough	4	1.7
Laryngeal edema	3	1.3
Unspecified	7	3.0
Gastrointestinal symptoms:	71	30.1
Abdominal pain	22	9.3
Diarrhea	20	8.5
Vomiting	16	6.8
Nausea	10	4.2
Heartburn	2	0.8
Flatulence	1	0.4
Unspecified	6	2.5
Other symptoms:	36	15.3
Hypotension	12	5.1
Tachycardia	13	5.5
Dizziness / light-headedness	10	4.2
Loss of consciousness	8	3.4
Malaise / fatigue	5	2.1
Sweating / chills	4	1.7
Anxiety	3	1.3
Palpitations	2	0.8
Paresthesia	2	0.8
Other[b]	7	3.0
Emergency department visit reported:		
Yes	20	8.5
No	216	91.5
Time to AGS symptom development reported consumption of meat or animal-based foods (n = 232)[c]:		
Yes	193	83.2
No	39	16.8
Methods used to diagnose AGS[a]:		
Clinician diagnosis	236	100.0
Serum IgE test:	235	99.6
ImmunoCAP assay	161	68.2
Streptavidin CAP	43	18.2
Other[d]	3	1.3
Not reported	73	30.9
Skin prick test	127	53.8
Oral food challenge	15	6.4
ImmunoCAP assay cut-point used to determine a positive AGS case (n = 161)[e]:		
≥0.35 kU_A/L	75	46.6
≥0.10 kUA/L	5	3.1
Not reported	81	50.3
α-Gal de-sensitization reported through consumption of small amounts of meat or animal-based foods during follow-up:		
Yes	7	3.0
No	229	97.0

[a] Multiple selections were possible for these variables, so percentages do not add to 100 %.
[b] One case each reported the following symptoms: blurred vision, dysphasia, edematous testicles, bradycardia, hypotonia, hypoxemia, and polyarthralgia.
[c] Percentages were tabulated out of the number of cases that reported reactions from consuming meat or animal-based foods (n = 232).
[d] Other tests used in one article each included: Western blot, Immulite XPI, and a radioallergosorbent test.
[e] Percentages were tabulated out of the number of cases that were assessed using the ImmunoCAP assay (n = 161).

Table 6
Summary characteristics of 21 observational studies that investigated post-tick exposure alpha-gal syndrome.

Study characteristics	No. of studies	% of studies
Population source[a]:		
Clinical allergy patients	20	95.2
General population	1	4.8
Occupational groups	1	4.8
Demographics reported[a]:		
Age	17	81.0
Gender	16	76.2
Ethnicity	3	14.3
None reported	4	19.0
α-Gal exposure methods reported[a]:		
Consumption of meat or meat by-products:	20	95.2
Beef	7	33.3
Pork	6	28.6
Lamb	4	19.0
Gelatin-containing product	4	19.0
Game meat	3	14.3
Other	3	14.3
Type of meat not reported	13	61.9
Pharmaceutical or cosmetic product	7	33.3
Consumption of dairy products	5	23.8
Tick species of exposure:		
Amblyomma americanum	1	4.8
Ixodes holocyclus	1	4.8
Not confirmed or reported	19	90.5
Time from last recalled tick exposure to AGS symptoms reported:		
Yes	3	14.3
No	18	85.7
AGS symptoms reported:		
Yes	18	85.7
No	3	14.3
Types of symptoms reported (n = 18)[a,b]:		
Anaphylaxis	14	77.8
Skin reactions:	16	88.9
Urticaria	15	83.3
Angioedema	10	55.6
Erythema	3	16.7
Pruritus	2	11.1
Subcutaneous nodules	1	5.6
Rash	1	5.6
Respiratory symptoms[c]	6	33.3
Gastrointestinal symptoms:	10	55.6
Diarrhea	3	16.7
Abdominal pain	2	11.1
Vomiting	2	11.1
Unspecified	7	38.9
Other symptoms:	10	55.6
Hypotension	4	22.2
Dizziness / light-headedness	3	16.7
Hypoxia	3	16.7
Loss of consciousness	3	16.7
Palpitations	1	5.6
Emergency department visits reported:		
Yes	2	9.5
No	19	90.5
Time to AGS symptom development reported after α-Gal exposure:		
Yes	10	47.6
No	11	52.4
Methods used to diagnose AGS[a]:		
Serum IgE test:	21	100.0
ImmunoCAP assay	16	76.2
Streptavidin CAP	6	28.6
Not reported	5	23.8
Clinician diagnosis	19	90.5
Skin prick test	6	28.6
Oral food challenge	4	19.0
Basophil activation assay	1	4.8
Self-diagnosis	1	4.8
ImmunoCAP assay cut-point used to determine a positive AGS case (n = 16)[d]:		
≥0.35 kU_A/L	9	56.3

(*continued on next page*)

Table 6 (*continued*)

Study characteristics	No. of studies	% of studies
≥0.10 kU_A/L	5	31.3
Not reported	2	12.5
Test sensitivity or specificity reported:		
Yes	3	14.3
No	18	85.7

[a] Multiple selections were possible for these variables, so percentages do not add to 100 %.

[b] Percentages were tabulated out of the number of articles that reported case symptoms (n = 18).

[c] Reported respiratory-related symptoms included bronchospasm and throat constriction in two studies, and the following in one study each: wheezing, dyspnea, swollen tongue, general respiratory distress, unspecified asthma-related symptoms, and unspecified.

[d] Percentages were tabulated out of the number of articles that reported using the ImmunoCAP assay (n = 16).

2019; Hilger et al., 2019; Platts-Mills et al., 2020a). Additional observational studies are needed to identify the prevalence, incidence, and distribution of AGS in different populations in North America and worldwide. For example, additional case-control studies and population-based cohort studies in high-risk regions for tick exposure could help to identify additional risk factors for AGS incidence and development.

Approximately two-thirds of the case reports described AGS among males, which corresponds with what has been reported for other tick-borne diseases (Openshaw et al., 2010; Schwartz et al., 2017). However, AGS patient populations reported in observational studies in the SR were not always predominantly male. While the age distribution of reported cases was skewed toward adults, observational studies reporting on cases in children and youth indicate that AGS can occur at any age (Kennedy et al., 2013; Mabelane et al., 2018). Other tick-borne diseases report a bimodal distribution in incidence by age group, with a small peak in those aged 5–9 years (Openshaw et al., 2010; Schwartz et al., 2017); further research should investigate possible under-reporting of AGS among this age group. Ethnicity was reported for only 77/236 of the cases and in 3/21 observational studies. Future studies should collect and report ethnicity data and aim to include diverse study populations to investigate possible socio-cultural differences in AGS prevalence and distribution. A wide variety of symptoms were reported among case reports and observational studies, with urticaria appearing to be the most common reaction. The presence of only gastrointestinal symptoms in some cases, as well as the delayed reaction, suggest the possibility for under-reporting and under-diagnosis of AGS. Given that anaphylaxis was a commonly reported outcome, efforts are needed to raise awareness about AGS among physicians and the public in tick-endemic areas.

Cases were primarily exposed to α-Gal through the consumption of red meat or other animal-based foods. There was considerable variability in the length of delay from food consumption to symptom development, with four cases reporting that some of their reactions occurred in less than 1 h, while others reported reactions ranging from one to several hours after a meal. Some case reports indicated that the time to AGS symptom development occurred within as little as 10 min, and that symptoms were more severe, after consumption of offal (e.g. pork or beef kidney) (Caponetto et al., 2013; Hodžić et al., 2019; Morisset et al., 2012). This is likely due to the presence of much higher levels of α-Gal in such products (Morisset et al., 2012). The delay in symptoms from the consumption of meat and other animal-based foods (e.g. milk) could be related to the length of time necessary to digest and absorb α-Gal-containing glycolipids (Platts-Mills et al., 2020a; Román-Carrasco et al., 2019), but this, as well as factors related to the differences in reported reaction times among AGS cases, is an area that requires further research.

While several studies have noted elevated levels of α-Gal-specific IgE among AGS patients (Fischer et al., 2020a; Kennedy et al., 2013; Mabelane et al., 2018; Mateo-Borrega et al., 2019; Wilson et al., 2019), positive α-Gal-specific IgE has also been found among a small proportion of the general population and in high-risk tick exposure groups (e.g. forest workers) despite rarely leading to AGS (Commins et al., 2011; Fischer et al., 2017; Venturini et al., 2018). For example, we identified only a single study that investigated the prevalence of AGS in a non-clinical population, which found that 1.7 % (5/300) of forest workers and hunters in Germany were positive for AGS (Fischer et al., 2017). Sufficiently high levels of α-Gal-specific IgE are likely needed to induce AGS in an individual (Fischer et al., 2017; Platts-Mills et al., 2020b). The threshold level to cause symptoms likely depends on a number of factors, such as host susceptibility (e.g. co-morbidities), socio-demographics, and environmental factors (Fischer et al., 2020a; Mateo-Borrega et al., 2019; Wilson et al., 2019). Further research is necessary to investigate the relationship between α-Gal-specific IgE levels and AGS development in different high-risk population groups (e.g. outdoor workers, individuals living in tick-endemic areas).

Observational studies in this SR varied in their use of α-Gal-specific IgE cut-points to determine positive AGS cases. Recommended cut-points for determining AGS include IgE values of ≥0.35 kU_A/L or ≥0.10 kU_A/L (Commins, 2020; Fischer et al., 2020a, 2017; Platts-Mills et al., 2020b). An AGS diagnosis is also suggested when α-Gal-specific IgE levels represent at least 1–2% of a patient's total IgE levels (Commins et al., 2014; Platts-Mills et al., 2020b). Only three studies in this SR reported on the diagnostic accuracy of their IgE immunoassay test. Li et al. (2018) conducted a retrospective analysis of sera from 118 AGS patients in a tick-endemic region of Australia, and found that the ≥0.35 kU_A/L cut-point yielded a sensitivity of 85 % and a specificity of only 32 % (Li et al., 2018). The authors questioned the utility of α-Gal-specific IgE testing as a diagnostic tool for AGS, as a patient's history of a tick bite was found to be a similar predictor of AGS (Li et al., 2018). Mabelane et al. (2018) evaluated diagnostic test performance in 84 South African AGS patients compared to a control population, finding that α-Gal-specific IgE levels ≥0.2 kU_A/L and an α-Gal/total IgE proportion of ≥0.75 % resulted in a positive predictive value of >95 %, but with sensitivities of 85 % and 88 % and specificities of 92 % and 88 %, respectively (Mabelane et al., 2018). Higher cut-points of ≥5.5 kU_A/L and an α-Gal/total IgE proportion of ≥2.12 % could detect ≥95 % of cases, with specificities of 96 % and 100 %, respectively, but resulted in a higher number of false negatives, with specificities of 68–69 % (Mabelane et al., 2018). A German study of allergy patients found that an optimal cut-point for diagnosing AGS was ≥0.54 kU_A/L, with a sensitivity of 96.5 % and specificity of 95 % (Fischer et al., 2020a). Additional research is necessary to investigate the accuracy and reliability of different diagnostic approaches to classifying AGS in different populations.

Tick exposure history was determined via patient self-reporting for all but one of the AGS cases (235/236). In addition, the proportion of AGS cases that recalled a tick exposure and the time since the most recently recalled tick bite were highly variable across studies. Self-reported, retrospective measurement of tick exposure is likely affected by recall bias, as individuals may not remember or know that they were bitten by a tick. Although only three experimental studies were identified in this SR, they provided further evidence to support that tick exposures lead to α-Gal-specific IgE sensitization and other AGS indicators. One cohort study evaluated changes in α-Gal-specific IgE levels among 67 AGS cases over time, comparing those who continued to report tick bites with those who reported no additional tick bites (Kim et al., 2020). The authors found a significant decrease in IgE levels among those who remained free of tick bites compared to those who continued to report tick bites (Kim et al., 2020), suggesting that AGS symptoms could decrease in severity or disappear if patients prevent exposure to additional tick bites. Further research in this area, as well as whether some AGS cases might be able to tolerate the consumption of small amounts of meat or animal-based foods, is warranted.

Table 7
Study-level characteristics of 21 observational studies that investigated post-tick exposure alpha-gal syndrome.

Study design and reference	Country	Population	Sample size	Percent female	Age (years)	Percent with AGS and recalling tick bites	Time from α-Gal exposure to symptoms	Time from tick exposure to AGS
Prevalence studies								
Commins et al. (2011)	U.S.	Allergy patients	125	NR	NR	All had AGS; >90 % had tick bites	NR	NR
Gadde et al. (2011)	U.S.	Allergy patients	11	64 %	Mean 46 (range: 16–71)	All had AGS and tick bites	NR	1 week to 2 years
Jerath et al. (2013)	U.S.	Allergy patients	100	48 %	Mean 49	All had AGS; 96 % had tick bites	Mean 5 h	NR
Kennedy et al. (2013)	U.S.	Allergy patients	51	31 %	Mean 12 (range: 4–17)	73 % had ASG, of which all had tick bites	Mean 4.68 h (range: 10 min to 24 h)	NR
Kiewiet et al. (2019)	Sweden	Allergy patients	137	50 %	Mean 49	All had AGS; 99 % had tick bites	NR	NR
Kimpel et al. (2019)	U.S.	Allergy patients	38	NR	NR	26 % had AGS; all had tick bite exposures	NR	NR
Li et al. (2018)	Australia	Allergy patients	118	NR	Range 7–83	22 % had AGS, of which all had tick bites	NR	NR
Merritt et al. (2011)	U.S.	Allergy patients	27	NR	NR	81 % had AGS, of which all had tick bites	NR	NR
Mullins et al. (2012)	Australia	Allergy patients	40	54 %	Median 48 (range: 18–78)	All had AGS; 60 % had tick bites	Median 3 h (range: 15 min to 9 h)	NR
Namba et al. (2018)	Japan	Allergy patients	52	23 %	Mean 66 (range: 27–90)	20 % had AGS, one of whom had tick bites	NR	NR
Renaudin et al. (2011)	France	Allergy patients	6	0 %	Mean 53.5 (SD: 16)	All had AGS and tick bites	Mean 5.5 h (range: 4–7)	NR
Thomas et al. (2017)	France	Allergy patients	19	16 %	Mean 47.5 (range: 18–73)	All had AGS; 47 % had tick bites	Mean 4.6 h (range: 2–12)	NR
Villalta et al. (2017)	Italy	Allergy patients	49	NR	NR	All had AGS; 55 % had tick bites	7.9 % <30 min; 10.5 % ≥30 min to 1 h; 13.1 % >1 h to 2 h; 60.6 % >2 h to 4 h; 7.9 % >4 h	1 to >12 months
Williams et al. (2015)	U.S.; Canada; Sweden; Australia	Allergy patients	226	22 %	Range 4–73	All had AGS (85 % physician-diagnosed); 82 % had tick bites	NR	NR
Van Nunen et al. (2009)	Australia	Allergy patients	25	72 %	Mean 29.9 (range: 21–63)	All had AGS and tick bites	40 % >4 h	1 to 6 months
Cross-sectional								
Mabelane et al. (2018)	South Africa	Allergy patients; general population (control)	84	67 %	Median 12 (range: 4–65)	All had AGS; 11 % had tick bites	Median 105 min (IQR: 85–135)	NR
Fischer et al. (2020a)	Germany	Allergy patients	1369	60 %	Median 43.4 (range: 0.6–89)	4.2 % had AGS; 73 % had tick bites	NR	NR
Fischer et al. (2017)	Germany	Forest workers and hunters; allergy patients (control)	300	11 %	Median 52 (IQR: 42–62)	1.7 % had AGS; 86 % had tick bites	NR	NR
Wilson et al. (2019)	U.S.	Allergy patients	261	54 %	Median 49 (range: 5–82)	All had AGS; 98 % had tick bites	10 % <1 h; 5% 1 to <2 h; 81 % ≥2 h	NR
Case-control								
Mateo Borrega et al. (2019)	Spain	Allergy patients	160 cases; 126 controls	48 %	Median 44 (IQR: 33–53)	All cases had AGS; 33 % had tick bites	Mean 240 min (IQR: 120–360)	NR
Cohort								
Kim et al. (2020)	U.S.	Allergy patients	67	52 %	Median 54 (range: 6–80)	All had AGS and tick bites	NR	NR

IQR = interquartile range; NR = not reported; SD = standard deviation.

In both case reports and observational studies, several AGS cases were reported to have a non-B blood group. It has been suggested that those with B and AB blood types might be less likely to develop AGS due to the similarity of α-Gal and the B antigen (Hamsten et al., 2013; Platts-Mills et al., 2020a). However, observational studies suggest that blood group may not be a consistent, relevant risk factor for AGS (Cabezas-Cruz et al., 2017; Mateo-Borrega et al., 2019). Further research is required to examine the possible influence of blood type, and other risk factors, on AGS development. Given the role of tick bites as the primary exposure leading to AGS (Fischer et al., 2020a; Mateo-Borrega

Table 8
Study-level characteristics of three experimental studies investigating post-tick exposure alpha-gal syndrome.

Study	Population	Tick exposure	α-Gal exposure	Outcomes measured	IgE test	Findings
Chandrasekhar et al. (2019)	Wild type mice, various strains, deficient in α-Gal	*A. americanum* tick saliva extract vs. saline (control) over 31 days	50 μg α-Gal-containing beef thyroglobulin in 100 μL distilled water	α-Gal specific IgE; core body temperature; mast cell protease levels; basophil activation	ELISA, 4 days post-exposure	Elevated α-Gal specific IgE in treated vs. control mice. Increased mast cell protease levels and basophils in treated vs. control mice post-challenge. No reduced temperature in treated or control mice.
Choudhary et al. (2019)	Wild type mice, C57Bl6/J, deficient in α-Gal	*A. americanum* tick saliva extract vs. saline (control) over 49 days	400 mg pork meat	α-Gal specific IgE; core body temperature	ELISA, 7 days post-exposure	Elevated α-Gal specific IgE in treated vs. control mice. Maximum temperature decrease 30 min post-challenge; no decrease in control mice.
Commins and Karim (2017)	Wild type mice (details not reported)	*A. americanum* tick saliva extract vs. saline (control) over 21 days	10 mg pork meat	α-Gal specific IgE; core body temperature; mast cell protease levels	ELISA, 7 days post-exposure	Elevated α-Gal specific IgE in treated vs. control mice. Maximum temperature decrease 130 min post-challenge; no decrease in control mice. Increased mast cell protease levels in treated vs. control mice post-challenge.

et al., 2019; Wilson et al., 2020), prevention and awareness efforts with the public should focus on the importance of avoiding tick exposures in tick-endemic areas. Research on Lyme disease prevention suggests that increasing public awareness of tick-borne diseases is an important predictive factor affecting people's likelihood to engage in tick prevention behaviours, such as tick checks and applying insect repellant (Aenishaenslin et al., 2017; Niesobecki et al., 2019). Socio-behavioural research is warranted to investigate the public's tick prevention behaviours and intentions in the context of their AGS knowledge and perceptions.

There are several limitations to this SR. Despite using a comprehensive search strategy, it is possible that some relevant articles could have been missed. Further, as the focus of this SR was only on post-tick exposure AGS, studies that reported on AGS without explicit tick exposures, or that focused only on immune responses from ticks without AGS development, were excluded. It is possible that such studies could have provided additional insights regarding the conclusions of this SR. Articles published in languages other than English were translated using Google Translate, which could have resulted in some errors. However, the impact of such errors should be minimal, as only five articles required translation. Given that AGS is an emerging condition, with the role of ticks first suggested in 2009, this SR would benefit from being updated again in 3–5 years to synthesize and integrate new published research knowledge. For example, since the completion of the search strategy, new research has reported that AGS cases appear to be less commonly reported in southern U.S. areas where imported fire ants are prevalent, possibly due to an antagonistic ecological relationship between fire ants and ticks (Wilson et al., 2020), which highlights additional complexities in the future distribution of AGS cases.

5. Conclusion

Cases of post-tick exposure AGS have been reported from countries worldwide since 2009. Evidence from case reports and series, observational studies, and experimental mice model studies suggest that tick bite exposures lead to α-Gal-specific IgE sensitization in humans, which can cause AGS. However, the specific mechanisms and risk factors that lead to AGS development require additional research. Different tick species have been linked to α-Gal-specific IgE reactions worldwide, with *A. americanum* being the primary species of exposure in North America and other species implicated elsewhere globally. It is also possible that other tick species or vectors might have the capacity to cause α-Gal-specific IgE sensitization; however, further research is needed in this area. With the predicted northward expansion of ticks due to climate change, it is likely that AGS cases will be identified in more northern U.S. states and in Canada in the coming years. However, due to the characteristic delay in reactions after consumption of α-Gal-containing foods, and the variability in symptoms and severity, cases are likely to be under-reported and under-diagnosed. There is a lack of agreement and consistency in the levels of α-Gal-specific IgE required for diagnosis of AGS; additional diagnostic test evaluation studies are needed. Further research is also warranted to investigate the epidemiology, incidence, distribution, and risk factors for AGS in the general population and in high-risk tick-exposure groups.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ttbdis.2021.101674.

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