Biomarkers for autoimmune disease diagnosis in the public health sector: A Systematic Review and Meta-Analysis

By

Zeena Morar

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Supervisors:

Prof. Mark E Engel PhD, Department of Medicine, UCT; SA Medical Research Council

Taariq Salie, Department of Medicine, University of Cape Town

Dr. Tasnim Bana, Department of Medicine, University of Cape Town

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Name: Zeena Morar

Student number: MRRZEE001

Signature: Signed by candidate

Date: 09/02/2024

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ABSTRACT

Rheumatic heart disease (RHD), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are autoimmune diseases with drastic effects on quality of life. Diagnostic challenges remain, especially given the prevalence of these diseases among people of low socioeconomic status. The purpose of this review was to determine, from published case-control and cross-sectional studies, whether selected protein biomarkers are discriminatory indicators of RHD, RA and SLE. This review was carried out in accordance with the Preferential Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A significant increase in adiponectin was found in patients with SLE and in patients with RA (including those with severe and mild cases of RA) as compared with healthy controls. Ficolin-3 was significantly upregulated in SLE patients and downregulated in RHD patients, while alpha-2-glycoprotein 1 was significantly upregulated in SLE patients compared to controls. Gelsolin was significantly downregulated in patients with RHD and in SLE patients with a flare-up and in remission. Given that data remain scant, further research into these proteins, along with others not previously identified, is warranted to evaluate their discriminatory power for the development of a cost-effective point-of-care diagnostic test.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADIPOQ	Adiponectin
ARA	American Rheumatism Association
ARF	Acute rheumatic fever
AUC	Area under the curve
AZGP1	Alpha-2-glycoprotein 1
C7	Complement C7
CI	Confidence interval
CRP	C-Reactive protein
D1GPLD1	Glycosylphosphatidylinositol specific phospholipase D1
ELISA	Enzyme-linked immunosorbent assay
EULAR	European League Against Rheumatism
FBLN1	Fibulin 1
FCN3	Ficolin-3
FLNB	Filamin B
GAS	Group A Streptococcus
GSN	Gelsolin
HIC	High income countries
IGFALS	Insulin like growth factor binding protein complex acid labile subunit
LMIC	Lower middle-income countries
MeSH	Medical Subject Headings
NOS	New-Castle Ottawa Scale
OLFM1	Olfactomedin 1
P4HB	Protein disulfide-isomerase
PRISMA	Preferential Reporting Items for Systematic Reviews and Meta-Analysis
PZP	Pregnancy zone protein
QSOX1	Quiescin sulfhydryl oxidase 1
RA	Rheumatoid arthritis
REMARK	Reporting recommendations for tumour MARKer prognostic studies
RHD	Rheumatic heart disease
RT-PCR	Reverse transcription polymerase chain reaction
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
Th1	T-helper 1 cell

CHAPTER 1 INTRODUCTION

Rheumatic heart disease (RHD) is an autoimmune disease that is endemic in many lower middle-income countries (LMIC) as well as within marginalized populations in high-income countries (HIC) (1–4). It is responsible for approximately 15 to 20 percent of heart failure cases within endemic countries (5). Being the most common cardiovascular disease in people under the age of 25 globally, these populations are impacted negatively in terms of their health and their socioeconomics (6–11). A total of 40 million people are affected by this disease with 0.31 million deaths in 2019, the majority of which are within the African continent. Of late, research conducted on RHD is considered a priority throughout the continent as highlighted in a recent publication of the African Union Communique for the eradication of RHD on the continent as well as the prioritization of the disease by the South African Medical Research Council (1,11,12).

The current understanding is that RHD develops initially through a Group A Streptococcal (GAS) infection, which contains epitopes which mimic heart muscle proteins that in turn drive a strong and inappropriate immune response, resulting in the development of acute rheumatic fever (ARF) (5–7). Untreated, recurrent episodes of ARF may result in permanent heart valve damage, which is then known as RHD (5–7). Inadequate access to healthcare, poor sanitation and overcrowding are considered risk factors that contribute to ARF (5,6,13). Much of the pathophysiology of this disease is unknown and interestingly, 75% of children with RHD have no record of previous ARF infection. It is suspected that RHD occurs at a subclinical level, reiterated in evidence that RHD cases present frequently with moderate to severe complications such as heart failure, pulmonary hypertension, stroke and infective endocarditis (3,6,7). Screening and diagnostic tests of high discriminatory power within the rural setting are thus incredibly important, as early detection of RHD can reduce morbidity and the need for surgical interventions (3).

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease whose prevalence varies amongst regions, ethnicities, age groups as well as socioeconomic divisions (14–17). Data seems to suggest that those of African descent might experience worse outcomes as well as have the highest prevalence and incidence within their populations (14–17). Thus, research conducted on SLE in Africa is needed to fill the gap in the literature. The lack thereof is in part due to underdiagnosing this complex disease but under-reporting of the African experience is an additional major contributor (17).

Connective tissue inflammation caused by SLE leads to a variety of clinical presentations, some of which include the heart (17). There is an increased mortality rate amongst patients diagnosed with SLE, with mortality of up to three times more than the general population. It is suspected that this

might even be higher in LMICs (14,15,17). Cardiovascular, renal and infectious diseases are the leading causes of morbidity and mortality amongst SLE patients, and the severity and course of the disease is determined, in part, by the socioeconomic status of the patient, which affects their access to medical care, clean water, and other resources (16,17). It is a difficult disease to diagnose because of its diverse clinical presentation and therefore, requires immunological assays for diagnosis (17). Genetic disposition, environmental factors, age, gender and hormonal status are thought to contribute towards the development of SLE (14–17).

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that leads to erosions, deformities, and functional loss of the joints. It affects up to 1% of adults globally with increased prevalence amongst women and in the elderly population (18–22). Rheumatoid arthritis has both a variable prevalence as well as disease course in LMIC, with Middle eastern and African countries having a prevalence estimated at between 0.06-3.4% (18,19). Studies have indicated that lower socioeconomic status and poor education increases the risk of developing RA, additionally being associated with poor prognosis (19,20). It is a disease that negatively affects physical, economic and emotional aspects of those who suffer from it (20).

There is a decrease in the quality of life and an increase in morbidity in those who experience chronic pain as well as progressive disability (19,22). Those who suffer from RA are at increased risk of mortality due to renal disease, infections, cardiovascular and respiratory disease (19,20). Additionally, patients have reduced life expectancy, similar to those with diabetes mellitus, Hodgkin's disease, stroke and coronary artery disease (20,22). Continuous treatment with disease-modifying anti-rheumatic drug therapies is necessary to delay disease progression. However, this treatment is costly and physically unpleasant due to its negative side-effects (22). Even a delay of only three months in diagnosis and treatment of RA can result in adverse long-term effects in the course of the disease (19). Many African countries do not have guidelines for the treatment of patients with RA, and healthcare workers have limited access to treatments (19). New therapies for the disease are not easily accessible in LMICs as they are expensive, and socio-economic conditions that predispose to endemic infections such as tuberculosis limit their use (18).

The diseases discussed above are more prominent and have worse prognoses within LMICs largely due to limitations in accessing healthcare, poor medical and social resources, lack of awareness, a deficiency in access to specialists and a lack of timely diagnosis and treatment (14,15,17–19). In order to diagnose these various conditions, the following is required; an echocardiogram for RHD, imaging for RA, and immunological studies for SLE (9,17,23). These methods of diagnosis require expensive equipment as well as a skilled healthcare worker to operate the machinery. Point-of-care diagnostic

tests with high discriminatory power would therefore allow for testing in rural and resource poor areas, enabling screening for and facilitating the diagnosis of these autoimmune diseases.

Autoimmune diseases trigger a self-perpetuating immune reaction which leads to tissue damage and chronic inflammation (24). Chronic inflammation results in an upregulation of certain proteins in the body as well as a downregulation of others.

Fourteen proteins, which together confer a 95% area under the curve (AUC), have been recently identified as having potential to distinguish cases of RHD, from controls (25). These potential biomarkers are Adiponectin (ADIPOQ), Complement C7 (C7), Quiescin sulfhydryl oxidase 1 (QSOX1), Pregnancy zone protein (PZP), Protein disulfide-isomerase (P4HB), C-Reactive protein (CRP), Filamin B (FLNB), Insulin like growth factor binding protein complex acid labile subunit (IGFALS), Ficolin-3 (FCN3), Glycosylphosphatidylinositol specific phospholipase D1 (D1GPLD1), Fibulin 1 (FBLN1), Alpha-2-glycoprotein 1 (AZGP1), Gelsolin (GSN) and Olfactomedin 1 (OLFM1). The mechanism of action of each protein is described below.

Adiponectin is an adipokine that is known to regulate insulin sensitivity, glucose levels and lipid metabolism. It achieves this via its anti-fibrotic, antioxidant and anti-inflammatory effects (26). It enhances glucose uptake and lipid metabolism by reducing gluconeogenesis and enhances fatty acid oxidation and glycolysis in the liver (27). Additionally, ADIPOQ stimulates the oxidation of fatty acids in skeletal muscle which reduces the accumulation of triglycerides (27). Adiponectin reduces inflammation in muscle cells, epithelial cells, and endothelial tissues. It protects against inflammation by enhancing insulin sensitivity (27). Adiponectin transcription is supressed by inflammatory cytokines such as interleukin 6 and tumour necrosis factor alpha (28).

Complement C7 forms part of the complement system which plays a part in the innate immune system. The complement system is involved in the opsonisation of pathogens and stimulates an inflammatory response in order to fight off infection (29). The complement system utilises C7 to protect against infection by creating a membrane attack complex which damages and creates holes in bacterial membranes (29). The complement system can be activated via three pathways. The classical pathway is activated either by the binding of the first protein in the complement cascade, C1q, directly to the surface of a pathogen or during an adaptive immune response whereby C1q binds to an antibody-antigen complex (29). The mannan-binding lectin pathway is activated by the binding of mannan-binding lectin to mannose-containing carbohydrates situated on the surface of pathogens (29). Lastly, the alternative pathway is initiated when complement protein C3b binds to the surface of a pathogen. It additionally amplifies the classical pathway of complement activation (29).

Both QSOX1 and P4HB are enzymes that are involved in the protein folding process through the formation of disulfide bonds (30,31). The enzymes oxidise thiols during the protein folding process which breaks down oxygen to hydrogen peroxide (32). This process is known as oxidative protein folding and occurs in the endoplasmic reticulum. One of the by-products of this process are chemicals called reactive oxygen species (33). If there is an excess accumulation of reactive oxygen species in the endoplasmic reticulum, oxidative stress occurs (33). This accumulation can lead to an inflammatory response.

Pregnancy zone protein is a protein that is elevated in conditions with high inflammation such as pregnancy (34). It is known to be a non-specific proteinase inhibitor yet evidence suggests that it may modulate T-helper cells (34,35). By inhibiting the activation of T-helper 1 (Th1) cells, PZP provides protection to the foetus from the maternal immune system (35). T-helper 1 cells produce cytokines that initiate pro-inflammatory responses for autoimmune reactions as well as to kill bacteria and viruses (24).

C-Reactive protein is produced by the liver in response to inflammatory cytokines (36). Levels of CRP in the body increase due to trauma, infection, and inflammation. Once these conditions cease, levels of CRP rapidly decrease in response (36). C-reactive protein interacts with Fc receptors on antibodies which leads to the production of pro-inflammatory cytokines which enhance the inflammatory response (36). Additionally, CRP opsonises bacteria for its destruction via the complement system (37). Due to its easy detection in blood, CRP is commonly used as a marker for inflammation through standard CRP testing (36,38).

Filamin B is an actin-binding protein as well as an RNA-binding protein. It plays a role in skeletal development by anchoring the actin network to transmembrane receptors and cellular membranes (39). RNA-binding proteins are involved in RNA splicing, stability, polyadenylation, localisation, translation, and degradation. Defects in RNA-binding proteins have been linked to immunologic disorders (39).

Insulin like growth factor binding protein complex acid labile subunit is a serum protein which binds insulin-like growth factors to increase their vascular localisation and half-life (40). Growth hormone stimulates the production of IGFALS and a deficiency of this protein results in delayed and slow puberty (40).

Ficolin-3 forms part of a protein group that consist of a fibrinogen-like domain and a collagen-like domain (41). Ficolin-3 was initially identified based on its reaction with sera from patients with SLE (41). This protein plays a role in the activation of the complement pathway, thus aiding the immune

system by activating the lectin pathway (41,42). Ficolin-3 mediates the clearance of late apoptotic cells and acts as an opsonin for phagocytosis (42).

Glycosylphosphatidylinositol specific phospholipase D1 is a high-density lipoprotein associated protein that may be involved in the metabolism of triglyceride-rich lipoproteins (43). The reduction of triglycerides may reduce insulin sensitivity and thus inflammation in the same way ADIPOQ does. Additionally, the reduction of D1GPLD1 decreases metastasis and inflammation in RA by modifying the activity of the NF-κB and Wnt/β-catenin pathways (44).

Fibulin 1 is part of a protein family of fibulins that are found in the extracellular matrix. It can be found in many extracellular structures such as basement membranes, microfibrils and elastic fibres (45). The widespread distribution enables them to bind with many inflammatory structures such as collagen, elastin, basement-membrane proteins, fibronectin and proteoglycans (45). Fibulins modulate cell proliferation and malignant transformation.

Alpha-2-glycoprotein 1 is a glycoprotein that can be found in endothelial cells, liver cells, macrophages, and neutrophils. The exact function of AZGP1 is unknown but it has been identified as an inflammatory protein found in human serum (46). It has been found to be upregulated in various autoimmune and benign inflammatory diseases such as asthma, RA, SLE and acute appendicitis in children (46).

Gelsolin is an extracellular isoform of gelsolin found in circulating blood and is responsible for removing actin filaments that have been released from dead cells into the blood (47). This mechanism protects the body from its own inflammatory response. Downregulated GSN levels have been observed in many inflammatory diseases such as RA, SLE and multiple sclerosis (47).

Olfactomedin 1 is a glycoprotein that is highly expressed in the retina and brain (48). It has four isoforms that are involved in the development and function of the nervous system and haematopoiesis (48,49). Olfactomedin proteins have been observed to assist in cell adhesion, protein-protein interactions and intercellular interactions (49). However, the exact function of OLFM1 is still unknown (48).

In attempting to develop a discriminatory test, we sought evidence, from published literature, for the ability of these biomarkers to discriminate RHD from the other autoimmune diseases mentioned above. In this systematic review, the performance of these 14 biomarkers in the context of RHD, SLE and RA will be determined and their ability to distinguish these diseases from each other. We expect that this knowledge could inform the development of a point-of-care diagnostic test of high discriminatory power that will enable early screening and diagnosis of these conditions.

Motivation for this work

The diagnosis of autoimmune diseases is difficult in LMICs, given the resource limitations including poor access to healthcare professionals and diagnostic tests. Additionally, guidelines used for the diagnosis of ARF has presented many challenges over the years. A low-cost discriminatory test for use in rural areas is needed especially for diseases of poverty such as RHD. Establishing an evidence base for recently-identified 14 putative biomarkers as being able to distinguish cases of severe RHD from controls, may serve to guide future endeavours towards a low-cost diagnostic test (25). A systematic review is required to determine if these biomarkers can discriminate between RHD and other systemic autoimmune diseases namely, SLE and RA.

Aim and objectives

Overall Aim

To determine the association between biomarkers and autoimmune diseases.

Research question

Which proteomic biomarkers are associated with autoimmune diseases?

Primary Objective

To determine the association of a set of 14 biomarkers with rheumatic heart disease, systemic lupus erythematosus, and rheumatoid arthritis.

Secondary Objective

To quantify the magnitude of the association between a set of 14 biomarkers and RHD, SLE and RA.

CHAPTER 2 METHODS

2.1 Study design

We utilised systematic review and meta-analysis methods. The protocol was submitted to and approved by the School of Public Health at the University of Cape Town and was also registered on PROSPERO with the ID number CRD42023390850. The methodology follows the scientific techniques and guidelines offered by the Preferential Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

2.2 Inclusion criteria

For inclusion, English language studies needed to have utilised mass spectrometry, enzyme-linked immunosorbent assay (ELISA), Luminex or reverse transcription polymerase chain reaction (RT-PCR) to detect biomarkers. Case-control and cross-sectional studies were eligible for inclusion. The autoimmune diseases included in the review are RHD, SLE and RA. The biomarkers reviewed included Adiponectin, Complement C7, Quiescin sulfhydryl oxidase 1, Pregnancy zone protein, Protein disulfide-isomerase, C-Reactive protein, Filamin B, Insulin like growth factor binding protein complex acid labile subunit, Ficolin-3, Glycosylphosphatidylinositol specific phospholipase D1, Fibulin 1, Alpha-2-glycoprotein 1, Gelsolin and Olfactomedin 1. All publications (irrespective of language) with English abstracts were included. Lastly, only protein studies conducted on humans were included.

2.3 Search strategy

A pre-determined search strategy was utilized for this review. Medical Subject Headings (MeSH) were used during the search for the biomarkers, study-designs, and diseases in question (Appendix A). The databases searched were PubMed, Scopus, and Web of Science. Google Scholar provided references to grey literature. Only protein case-control and cross-sectional studies conducted on humans were included as they were relevant to the overall aim of the review. No restriction was placed on the date of publication, nor the location of publication. The search was conducted between the 14th and the 18th of January 2023. Additional articles were found during the screening process.

2.4 Screening of articles

All the articles found were uploaded and managed with the Rayyan platform (50). The screening process was performed in duplicate by two independent reviewers. The articles were screened using pre-determined selection criteria as specified above. Reviewers T.S. and Z.M. had a discrepancy with 34 studies. These were referred to M.E. for arbitration for final selection.

2.5 Data extraction

Data extraction was performed independently by two reviewers in duplicate. A piloted, standardised data extraction form was used (Appendix C). Both quantitative and qualitative data were extracted from the studies. The first author, year of publication, journal and publication type were recorded for each of the studies. Study design, disease studied, and biomarker studied were recorded in order to categorise the studies during statistical analysis. Comorbidities that differentiated between cases and controls in case-control studies were noted as it affects the comparability of results. The laboratory method used was recorded as well in order to compare the accuracy between methods of biomarker measurement. The classification for disease used was recorded to verify the accuracy and consistency of disease classification between studies.

Aspects of the study design such as location, sex, average age, and BMI of participants were noted to assess any outliers if they appeared during the meta-analysis stage. Additionally, the income status of the country each study was conducted in were determined at the time of each articles' publication for outlier assessment. This data was taken from the World Bank database for country classifications by income level (51). For the purpose of meta-analysis, the total number of study participants, number of controls and cases and biomarker measurements were extracted from the included articles. These same variables were recorded for any sub-groups that were studied as well. The overall outcome was noted for the studies that could not be part of the meta-analysis and were instead included in the narrative portion of the review.

2.6 Statistical analysis

Meta-analysis was performed on the case-control studies that contained all the necessary data for analysis. RStudio version 4.1.0 was used in conjunction with the following packages: forestplot, meta, metafor, and readxl. A p-value of ≤ 0.05 was regarded as significant. Biomarker measurements of the means and standard deviations were converted to µg/ml for comparability. Medians, ranges, and interquartile ranges were converted into means and standard deviations using the methods proposed by Luo, et al, and Wan, et al (52,53). Biomarker values were rounded to 4 decimal places unless the value was extremely small in which case, they were then rounded to 5 decimal places. As the association between protein upregulation and downregulation and disease was the primary aim of this study, mean difference was calculated. Ninety-five percent confidence intervals (CI) were used. Heterogeneity was evaluated using Higgins I^2 test. The Higgins I^2 test was interpreted as follows: 0% indicates no heterogeneity, 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, 75% indicates high heterogeneity, and 100% indicates maximum heterogeneity. Due to varying clinical and methodological characteristics, heterogeneity was expected; hence we employed a random

effects model during the statistical analysis stage to account for variance within and between studies and attributed equal weight to each study.

Studies were categorised according to disease and biomarker. Furthermore, subgroup analyses were conducted based on disease severity and disease activity. The mean difference between cases and controls in studies were calculated and compared within each category and subgroup. Forest plots were generated for visualisation. Any outliers detected were removed to observe their effect on the overall outcome. Outliers were defined as studies with a mean difference exceeding 20 units above or below the overall group mean difference, as well as studies that presented the only negative mean difference within the group. Due to the large number of studies measuring ADIPOQ in RA, the studies were ordered according to the income status of the country the study was performed in. This approach would have allowed us to identify trends, as income status possibly reflects the resources available within those countries. All of the subgroups were compared to their pooled categories to determine the discriminatory power of the biomarkers for the autoimmune disease of interest.

2.7 Risk of bias

There is currently no validated tool to measure the quality of studies investigating surrogate biomarkers as outcome measures. Therefore we used an adapted questionnaire based on the assay methods and study design sections of the Reporting recommendations for tumour MARKer prognostic studies (REMARK) by McGhee, et al (54). We combined the REMARK quality criteria with the New-Castle Ottawa Scale (NOS) which is used to assess the quality of non-randomised studies (55). In doing so we developed our own tool to assess studies examining surrogate biomarkers as outcome measures (Appendix D).

Quality assessment was conducted by two independent reviewers in duplicate. Studies were assessed on the quality of study design, biomarker measurement, participant selection and statistical analysis (Table 2). The studies were rated on a scale of 1-13. A score of 1-5 indicated a high risk of bias, 6-10 a moderate risk of bias and 11-13 a low risk of bias. A study with a low risk of bias is considered to be of high-quality and a study with a high risk of bias to be of low-quality.

2.8 Ethics

As this is a systematic review which utilises secondary data from published studies, an ethics waiver along with a research proposal was submitted for review and subsequently approved by the School of Public Health Departmental Research Committee, Faculty of Health Sciences, the University of Cape Town. A waiver for ethics approval was obtained from the committee (Appendix G).

CHAPTER 3 RESULTS

3.1 Overview of search strategy and included articles

The Rayyan online platform was used to manage the search results. Of the 3070 articles found, 774 duplicate articles were removed, together with nine articles during the search. During the screening process, were excluded as they were detected as duplicates and ineligible by Rayyan's automation tools. A further 2110 articles did not meet the selection criteria and were deemed irrelevant. Seven-hundred and forty-seven studies on CRP were excluded, given that CRP is non-specific as it is upregulated in many diseases that involve inflammation; this review aimed to identify alternative biomarkers that could potentially be discriminatory. Of the 14 target biomarkers, as described in the introduction, 13 were present in articles potentially relevant to this review. Twenty-one articles could not be retrieved (not open access, not available via the UCT library and the authors could not be reached) leaving 156 articles being reviewed for inclusion. During this process, an additional three studies were found from grey literature and reviewed. After full text review a total of 54 articles were included for data extraction (Table 1). The overall screening process is detailed in Figure 1.

3.2 Study characteristics

Characteristics of the included studies are presented in Table 1. The 54 included studies, comprising 47 case-control studies and seven cross-sectional studies, were all journal articles published between 2006 and 2022. Two studies evaluated RHD while, RA and SLE were evaluated in 36 and 16 studies, respectively. Only four of the 13 biomarkers were examined in the included articles, namely ADIPOQ (n= 42 studies) , GSN (7 studies), FCN3 (4 studies) and AZGP1 (one study).

All of the included studies varied in location, income status of country, year of publication, sex, and age of study participants. The majority of studies measured biomarkers using ELISA, with four utilising Luminex and one utilising mass spectrometry. The phenotype of the diseases in question were not specified in any of the included studies. The guidelines used for disease classification were all standardised and of approved methods (Table 1).

Figure 1. PRISMA flow diagram

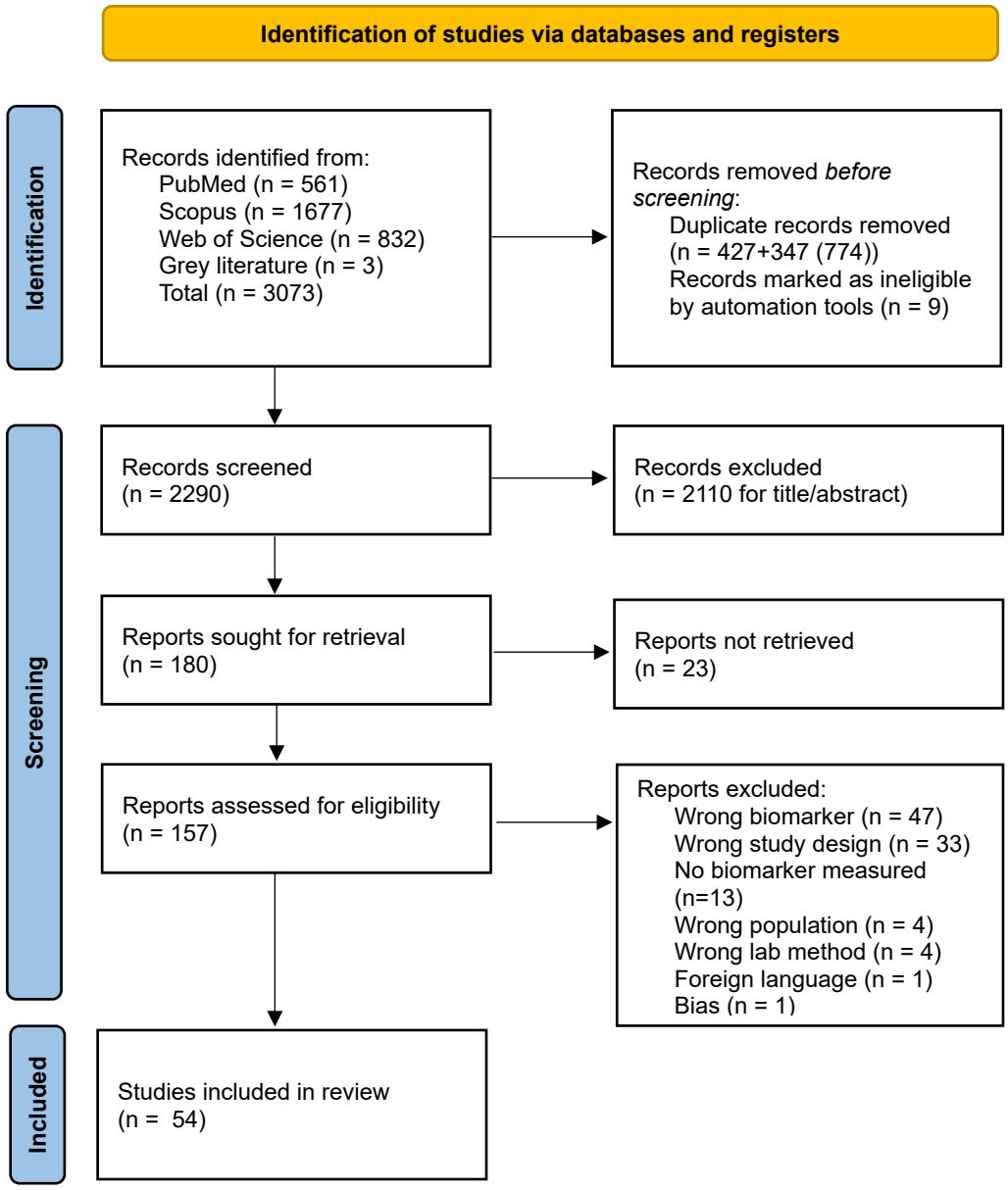


Table 1. Characteristics of included studies

Study ID	Study design	Country	Disease	Diagnostic criteria	Biomarker	Laboratory method	Total participants	Average age of participants (years)
Alkady, et al. 2011 (56)	Case-control	Egypt	RA	1987 revised ACR criteria	ADIPOQ	ELISA	Cases (n = 70), Controls (n = 30)	Cases 48.12, Controls 46.44
Andersen, et al. 2009 (57)	Case-control	Denmark	SLE	1982 revised criteria for classification of SLE	FCN3	ELISA	Cases (n = 95), Controls (n = 103)	Cases 38, Controls 38
Argun, et al. 2014 (47)	Case-control	Turkey	RHD	Modified Jones criteria for ARF revised 1992 & the WHO's echo-cardiographic criteria for carditis	GSN	ELISA	Cases (n = 37), Controls (n = 24)	Cases 11, Controls 11.8
Barbosa, et al. 2015 (58)	Case-control	Brazil	SLE	ACR classification criteria for SLE	ADIPOQ	ELISA	Cases (n = 52), Controls (n = 33)	Cases 33.4, Controls 32.5
Borman, et al. 2018 (59)	Cross-sectional	Turkey	RA	2010 ACR classification criteria	ADIPOQ	ELISA	55	53.5
Catarino, et al. 2021 (60)	Case-control	Brazil	RHD	Jone's modified criteria & transthoracic echocardiogram	FCN3	ELISA	Cases (n = 76), Controls (n = 63)	Cases 37, Controls 37
Chamorro-Melo, et al. 2022 (61)	Case-control	Colombia	RA	ACR/EULAR 2010 disease criteria	ADIPOQ	Luminex	Cases (n = 51), Controls (n = 51)	Cases median 52, Controls median 52
Chen, et al. 2022 (62)	Cross-sectional	China	RA	1987 ACR classification criteria	ADIPOQ	ELISA	125	55.7
Chihara, et al. 2020 (63)	Case-control	Japan	RA	1987 ACR/EULAR diagnostic criteria	ADIPOQ	ELISA	Cases (n = 136), Controls (n = 78)	Cases 69.6, Controls 66.7
Chougule, et al. 2018 (64)	Case-control	India	SLE	2015 ACR-SLICC revised criteria for diagnosis of SLE	ADIPOQ	ELISA	Cases (n = 60), Controls (n = 40)	Cases 28.53, Controls 28.53

Chung, et al. 2009 (65)	Case-control	USA	SLE	1982 revised criteria for classification of SLE	ADIPOQ	ELISA	Cases (n = 109), Controls (n = 78)	Cases 40.2, Controls 40.5
DeClercq, et al. 2017 (66)	Case-control	Canada	RA	self-reported	ADIPOQ	Luminex	Cases (n = 80), Controls (n = 80)	Cases 60.3, Controls 57.7
Dessein, et al. 2013 (67)	Case-control	South Africa	RA	1988 ACR criteria for RA	ADIPOQ	ELISA	Cases (n = 119), Controls (n = 77)	Cases 55.8, Controls 56.5
Diaz-Rizo, et al. 2017 (68)	Case-control	Mexico	SLE	1982 ACR criteria for SLE	ADIPOQ	ELISA	Cases (n = 103), Controls (n =83)	Cases 42.6, Controls 44.6
Ebina K, et al. 2009 (69)	Case-control	Japan	RA	1987 revised ACR criteria	ADIPOQ	ELISA	Cases (n = 90), Controls (n = 42)	Cases 60.8, Controls 61.7
El-Batch, et al. 2010 (70)	Case-control	Egypt	RA	1987 ACR revised criteria for the diagnosis of RA	ADIPOQ	ELISA	Cases (n = 30), Controls (n = 15)	Cases 49.4, Controls 48.1
El-Hini, et al. 2013 (71)	Case-control	Egypt	RA	ACR criteria for the diagnosis of RA	ADIPOQ	ELISA	Cases (n = 40), Controls (n = 40)	Cases 32.82, Controls 33.64
Gamez-Nava, et al. 2020 (72)	Case-control	Mexico	SLE	1982 ACR criteria for SLE	ADIPOQ	ELISA	Cases (n = 196), Controls (n = 52)	Cases median 27.3, Controls median 27.9
Giles, et al. 2011 (73)	Cross-sectional	USA	RA	the ARA 1987 revised criteria for the classification of RA	ADIPOQ	ELISA	152	59
Gonzalez-Gay, et al. 2008 (74)	Cross-sectional	Spain	RA	1987 ACR for RA	ADIPOQ	ELISA	33	55
Hein, et al. 2014 (75)	Case-control	Denmark	SLE	ACR criteria for SLE	FCN3	ELISA	Cases (n = 68), Controls (n = 29)	40.1
Kang, et al. 2014 (76)	Case-control	South Korea	RA	1987 ACR for RA	GSN	ELISA	Cases (n = 30), Controls (n = 30)	Cases median 55, Controls median 55
Lee, et al. 2019 (77)	Case-control	South Korea	RA	not specified	GSN	Mass spec	Cases (n = 41), Controls (n = 93)	Cases 55.4, Controls 57
Lei, et al. 2020 (78)	Case-control	China	RA	2010 ACR criteria	ADIPOQ	ELISA	Cases (n = 60), Controls (n = 29)	Cases 53.77, Controls 51

Li, et al. 2015 (79)	Case-control	China	RA	1987 revised ACR criteria	ADIPOQ	ELISA	Cases (n = 180), Controls (n=160)	Cases 42.13, Controls 43.11
Mahieu, et al. 2018 (80)	Cross-sectional	USA	SLE	1982/1997 updated ACR classification criteria for SLE	ADIPOQ	Luminex	129	45.5
Manrique-Arija, et al. 2016 (81)	Case-control	Spain	RA	2010 ACR/EULAR classification criteria	ADIPOQ	ELISA	Cases (n = 46), Controls (n = 45)	Cases 51.6, Controls 50.7
Markula-Patjas, et al. 2014 (82)	Case-control	Finland	RA	International League of Associations for Rheumatology classification of juvenile idiopathic arthritis, second revision	ADIPOQ	ELISA	Cases (n = 44), Controls (n = 89)	Cases 14.2, Controls 13.9
Mosaad, et al. 2022 (83)	Case-control	Egypt	SLE	2019 ACR/EULAR classification criteria for SLE	GSN	ELISA	Cases (n =50), Controls (n =30)	Cases 38.5, Controls 37.8
Mun, et al. 2018 (84)	Case-control	South Korea	RA	not specified	GSN	ELISA	Cases (n = 44), Controls (n = 43)	Cases 59.8, Controls 60.1
Nicolaou, et al. 2018 (85)	Case-control	Cyprus	RA	2010 ACR/EULAR classification criteria	ADIPOQ	ELISA	Cases (n = 30), Controls (n = 15)	Cases 56.33, Controls 53.80
Oranskiy, et al. 2012 (86)	Case-control	Russia	RA	Seropositive for RA	ADIPOQ	ELISA	Cases (n = 39), Controls (n = 20)	Cases median 53, Controls median 52
Otero, et al. 2006 (87)	Case-control	Spain	RA	ACR classification criteria	ADIPOQ	ELISA	Cases (n = 31), Controls (n = 18)	Cases 46.1, Controls 48.3
Ozgen, et al. 2010 (88)	Case-control	Turkey	RA	1987 ARA revised criteria for the classification of RA	ADIPOQ	ELISA	Cases (n = 56), Controls (n = 29)	Cases 52.9, Controls 38
Park, et al. 2016 (89)	Case-control	South Korea	RA	1987 ACR criteria for RA	GSN	ELISA	Cases (n = 264), Controls (n=187)	Cases 53.2, Controls 52.9
Parra, et al. 2020 (90)	Case-control	Spain	SLE	1997 ACR revised classification criteria for SLE	GSN	ELISA	Cases (n = 104), Controls (n = 46)	Cases 48.8, Controls 48.7

Plawecki, et al. 2016 (91)	Case-control	France	SLE	1997 revised ACR classification criteria for SLE	FCN3	ELISA	Cases (n = 165), Controls (n = 48)	Cases 44, Controls 41
Popa, et al. 2009 (92)	Case-control	Netherlands	RA	ACR criteria	ADIPOQ	ELISA	Cases (n = 58), Controls (n = 58)	Cases 56, Controls 55
Qian, et al. 2018 (93)	Case-control	China	RA	2010 ACR/EULAR classification criteria	ADIPOQ	ELISA	Cases (n = 38), Controls (n = 20)	Not stated
Reynolds, et al. 2010 (94)	Case-control	USA	SLE	1982 ACR revised criteria for SLE	ADIPOQ	ELISA	Cases (n = 119), Controls (n = 71)	Cases 42.6, Controls 41.3
Rezaieyazdi, et al. 2020 (95)	Case-control	Iran	SLE	SLICC criteria for SLE	ADIPOQ	ELISA	Cases (n = 59), Controls (n = 31)	Cases 30.8, Controls 34.2
Rodriguez, et al. 2020 (96)	Case-control	Colombia	RA	2010 ACR/EULAR classification criteria	ADIPOQ	Luminex	Cases (n = 51), Controls (n = 51)	Cases 48.55, Controls 48.55
Sada, et al. 2006 (97)	Case-control	Japan	SLE	ACR diagnostic criteria for SLE	ADIPOQ	ELISA	Cases (n = 37), Controls (n = 80)	Cases 44, Controls 44
Seewordova, et al. 2016 (98)	Case-control	Russia	RA	2010 EULAR/ARA criteria	ADIPOQ	ELISA	Cases (n = 88), Controls (n = 45)	Cases median 42, Controls median 42
Senolt, et al. 2006 (99)	Case-control	Czech Republic	RA	1987 ACR revised criteria for the diagnosis of RA	ADIPOQ	ELISA	Cases (n = 20), Controls (n = 23)	Cases 57.15, Controls 58.13
Sirenko, et al. 2016 (100)	Case-control	Ukraine	RA	EULAR 2010	ADIPOQ	ELISA	Cases (n = 42), Controls (n = 20)	Cases 54, Controls <54
Tan, et al. 2009 (101)	Case-control	China	RA	1987 ACR criteria for RA	ADIPOQ	ELISA	Cases (n = 35), Controls (n = 20)	Cases median 48.5, Controls median 45.9
Targonska-Stepniak, et al. 2010 (102)	Cross-sectional	Poland	RA	1987 ARA revised criteria for the classification of RA	ADIPOQ	ELISA	80	53.7
Targonska-Stepniak, et al. 2022 (103)	Cross-sectional	Poland	RA	ACR/EULAR classification criteria for RA	ADIPOQ	ELISA	109	54

Vadacca, et al. 2013 (104)	Case-control	Italy	SLE	Hocheberg's modified ACR classification criteria for SLE	ADIPOQ	ELISA	Cases (n = 60), Controls (n = 29)	Cases 42.26, Controls 45.69
Veluri, et al. 2019 (105)	Case-control	India	RA	2010 ACR/EULAR classification criteria	ADIPOQ	ELISA	Cases (n = 40), Controls (n = 30)	Cases 46.30, Controls 44.77
Yang, et al. 2020 (46)	Case-control	China	SLE	2003 International Society of Nephrology/Renal Pathology Society classification criteria for Lupus nephritis	AZGP1	ELISA	Cases (n = 101), Controls (n = 21)	Cases median 29, Controls median 31
Yoshino, et al. 2010 (106)	Case-control	Japan	RA	1987 ACR revised criteria for the diagnosis of RA	ADIPOQ	ELISA	Cases Female 110, Controls Female 124, Cases Male 141, Controls Male 146	Cases Female 59, Controls Female 57.5, Cases Male 61, Controls Male 45.6
Young, et al. 2009 (28)	Case-control	USA	RA	ACR	ADIPOQ	ELISA	Cases (n = 167), Controls (n = 91)	Cases 54.2, Controls 53.3

3.3 Risk of bias results

Out of the 54 included studies, 15 had a high risk of bias, 37 had a moderate risk of bias and two had a low risk of bias (Table 2). Out of the 15 high risk of bias studies, two were analysed in the meta-analysis and the rest were included in the narrative portion of the review. Majority of the included studies lacked a power calculation, mention of an appropriately sized study population, definition of controls and there was no blinding during biomarker measurement in all but three studies. Most of the included studies however, had a scientifically valid reason for evaluating the given biomarker for investigation, used an appropriate method to measure biomarker concentration which was ELISA and utilised valid and reliable criterion for diagnosis (Table 1). The high risk of bias studies mainly lacked factors contributing to the confidence of their data, the comparability between groups was weak and the statistical association between groups was insufficient. The low risk of bias studies either did not perform a power calculation and mention if an appropriately sized study population was used or did not have a primary aim to validate a biomarker for disease diagnosis and did not blind during biomarker measurement.

3.4 Meta-analysis

Thirty-two case-control studies were included in the meta-analysis (Table 3). The remaining 15 case-control studies had results not amenable to statistical analysis. Additionally, a single study had results separated into males and females. While meta-analysis was performed on females' data, the males' results were not amenable to statistical analysis. Therefore, seven cross-sectional studies as well as the 16 case-control studies were included in the narrative portion of the review. Additional forest plots can be found in Appendix E.

Table 2. Summary of risk of bias assessment of all included studies in the systematic review

Study	A			B					C			D		Quality Score
	A1	A2	A3	B1	B2	B3	B4	B5	C1	C2	C3	D1	D2	
Alkady et al., 2011	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Andersen, et al. 2009	1	1	1	0	1	0	0	0	0	0	1	0	1	6
Argun, et al. 2014	1	1	1	0	1	0	0	0	1	0	1	0	1	7
Barbosa, et al. 2015	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Borman, et al. 2018	0	1	1	0	1	0	0	0	1	0	0	0	0	4
Catarino, et al. 2021	1	1	1	1	1	0	0	0	0	0	0	1	0	6
Chamorro-Melo, et al. 2022	0	1	1	0	1	1	1	0	1	1	1	0	1	9
Chen, et al. 2022	0	1	1	1	1	0	0	0	1	0	0	1	0	6
Chihara, et al. 2020	0	1	1	1	1	0	0	0	1	1	0	1	1	8
Chougule, et al. 2018	0	1	1	0	1	0	0	0	1	0	1	0	0	5
Chung, et al. 2009	1	1	1	1	1	0	0	0	1	1	1	1	1	10
DeClercq, et al. 2017	1	1	1	1	0	0	0	0	0	0	1	1	0	6
Dessein, et al. 2013	1	1	1	1	1	0	0	0	0	0	1	1	1	8
Diaz-Rizo, et al. 2017	1	1	1	1	1	0	0	1	1	1	1	1	1	11
Ebina K, et al. 2009	0	1	1	1	1	0	0	0	1	0	1	1	1	8
El-Batch, et al. 2010	0	1	1	1	1	0	0	0	1	0	1	0	1	7
El-Hini, et al. 2013	0	1	1	1	1	0	0	0	1	0	1	1	1	8

Gamez-Nava, et al. 2020	0	1	1	1	1	0	0	1	1	1	1	1	1	10
Giles, et al. 2011	0	1	1	1	1	0	0	0	0	0	0	1	0	5
Gonzalez-Gay, et al. 2008	0	1	1	1	1	0	0	0	1	0	0	1	0	6
Hein, et al. 2014	0	1	1	1	1	0	0	0	0	0	0	1	0	5
Kang, et al. 2014	1	1	1	0	1	0	0	0	1	0	0	0	0	5
Lee, et al. 2019	1	1	1	0	0	0	0	0	0	0	0	0	0	3
Lei, et al. 2020	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Li, et al. 2015	1	1	1	1	1	0	0	0	1	1	1	1	1	10
Mahieu, et al. 2018	0	1	1	1	1	1	0	0	1	0	0	1	0	7
Manrique-Arija, et al. 2016	0	1	1	1	1	1	1	0	1	1	1	1	1	11
Markula-Patjas, et al. 2014	1	1	1	1	1	0	0	0	1	0	1	1	1	9
Mosaad, et al. 2022	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Mun, et al. 2018	1	0	1	0	0	0	0	0	0	1	0	0	0	3
Nicolaou, et al. 2018	1	0	1	1	1	0	0	0	0	0	0	0	1	5
Oranskiy, et al. 2012	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Otero, et al. 2006	1	1	1	0	1	0	0	0	0	0	1	0	1	6
Ozgen, et al. 2010	0	1	1	1	1	0	0	0	0	0	0	1	1	6
Park, et al. 2016	0	1	1	1	1	0	0	0	1	1	0	1	0	7
Parra, et al. 2020	0	1	1	1	1	0	0	0	0	0	1	1	1	7

Plawecki, et al. 2016	1	1	1	0	1	0	0	0	0	0	1	0	0	5
Popa, et al. 2009	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Qian, et al. 2018	0	1	1	0	1	0	0	0	0	0	0	0	0	3
Reynolds, et al. 2010	0	1	1	1	1	0	0	0	0	0	1	1	1	7
Rezaieyazdi, et al. 2020	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Rodriguez, et al. 2020	1	1	1	1	1	0	0	0	1	0	1	1	0	8
Sada, et al. 2006	0	1	1	0	1	0	0	0	1	0	1	0	1	6
Seewordova, et al. 2016	1	1	1	0	1	0	0	0	1	1	1	0	1	8
Senolt, et al. 2006	1	1	1	1	1	0	0	0	0	0	0	1	1	7
Sirenko, et al. 2016	0	0	1	0	1	0	0	0	0	0	1	0	0	3
Tan, et al. 2009	1	1	1	1	1	0	0	0	0	0	0	1	0	6
Targonska-Stepniak, et al. 2010	0	1	1	1	1	0	0	0	0	0	0	1	0	5
Targonska-Stepniak, et al. 2022	0	1	1	1	1	0	0	0	0	0	0	1	0	5
Vadacca, et al. 2013	0	1	1	1	1	0	0	0	1	1	1	0	0	7
Veluri, et al. 2019	0	1	1	0	1	1	1	0	1	0	1	0	1	8
Yang, et al. 2020	1	1	1	0	1	1	0	0	0	0	0	0	0	5
Yoshino, et al. 2010	0	1	1	1	1	0	0	0	0	0	0	1	0	5
Young, et al. 2009	0	1	1	1	1	0	0	1	0	1	1	1	1	9
A. Biomarker selection. A1: Primary aim to validate biomarker, A2: Reason for evaluating biomarker, A3: Was an appropriate method used to measure biomarker concentration														

B. Factors contributing to confidence of data. B1: Has confounding factors been taken into consideration, B2: Reliable criterion for diagnosis, B3: Power calculation completed, B4: Was the included number of participants appropriate, B5: Was measurement of biomarker blinded to patient demographics
C. Comparability between groups. C1: Selection of cases unbiased, C2: Definition of controls, C3: Confounding factors between groups equal
D. Statistical associations between groups. D1: Associations made using statistical modelling, D2: Sufficient detail of analyses
1. Study met the criteria; 0. Study did not meet the criteria
Quality score. Blue: Low risk of bias, Purple: Moderate risk of bias, Orange: High risk of bias
(Refer to Appendix D for the detailed questions posed for each domain)

3.4.1 Adiponectin in rheumatoid arthritis

Twenty-one studies measured ADIPOQ in patients with RA and controls. Adiponectin was measured in µg/ml by ELISA for many of the studies apart from Chamorro-melo, et al which used Luminex. There was a significant increase in ADIPOQ in patients with RA compared to healthy controls (mean difference = 7.1407; 95% CI [2.0373; 12.2440]; p = 0.0061; I^2 = 100%) (Figure 2). Removal of outliers Ozgen, et al and Seewordova, et al reduced the mean difference to 3.9815 (95% CI [1.0505; 6.9125]; p = 0.0078; I^2 = 99.6%). Two studies (Nicolaou, et al and Yoshino, et al) were determined to be of a high risk of bias and were consequently removed. Meta-analysis of the remaining 17 studies determined that ADIPOQ is significantly increased in patients with RA compared to healthy controls (mean difference = 3.6334; 95% CI [0.2802; 6.9867]; p = 0.0337; I^2 = 99.7%) (Figure 3).

3.4.1.1 Severe rheumatoid arthritis vs controls

There was a significant increase in ADIPOQ levels in severe cases of RA compared to controls (mean difference = 8.6; 95% CI [6.4612; 10.7388]; p < 0.0001) according to one study.

3.4.1.2 Mild rheumatoid arthritis vs controls

Meta-analysis of a single study revealed a statistically significant increase in ADIPOQ levels in mild cases of RA compared to controls (mean difference = 4.8; 95% CI [2.4110; 7.1890]; p < 0.0001).

3.4.1.3 Active rheumatoid arthritis vs controls

The pooled mean difference of the three studies evaluating ADIPOQ in active rheumatoid arthritis patients compared to healthy controls was not statistically significant (mean difference = 14.1043; 95% CI [-2.6316; 30.8402]; p = 0.0986; I^2 = 100%). Removal of Veluri, et al produced a statistically significant mean difference of 21.2522 (95% CI [5.2009; 37.3035]; p = 0.0095; I^2 = 98.9%), although the 95% confidence interval is imprecise. With the removal of the outlier ADIPOQ was significantly increased in cases with active RA.

3.4.1.4 Cases in remission vs controls

Three studies had a combined mean difference of 5.3388 (95% CI [-0.5476; 11.2252]; p=0.0755; I^2 = 99.9%). This indicates an insignificant increase in ADIPOQ levels in remission cases compared to healthy controls. By removing the outlier (Veluri, et al 2019), the results become statistically significant, and the magnitude of effect increases to 8.3293 (96% CI [4.4761; 12.1825]; p < 0.0001, I^2 = 85.3%), revealing ADIPOQ to be significantly upregulated in RA patients in remission compared to healthy controls.

3.4.2 Adiponectin in systemic lupus erythematosus

Seven studies evaluated the levels of ADIPOQ in patients with SLE compared to healthy controls. Adiponectin levels were measured in µg/ml using ELISA across all the studies. The pooled mean difference was determined to be 3.6426 (95% CI [1.7126; 5.5727]; p = 0.0002; I^2 = 93.5%) (Figure 4). This suggests that ADIPOQ is significantly increased in SLE patients compared to controls. The narrow 95% confidence interval indicates precision despite the I^2 value indicating high heterogeneity. Barbosa, et al was determined to be an outlier and was removed from the analysis, the magnitude of effect became 3.7759 (95% CI [1.8439; 5.7078]; p= 0.0001; I^2 = 94.3%). The outlying results from Barbosa, et al did not seem to influence the overall mean difference.

3.4.2.1 Active systemic lupus erythematosus vs controls

The study by Barbosa, et al calculated mean difference to be -29.3 (95% CI [-69.2097; 10.6097]; p = 0.1502). This suggests that ADIPOQ is decreased in patients with active SLE compared to healthy patients however not significant.

3.4.2.2 Inactive systemic lupus erythematosus vs controls

The study by Barbosa, et al calculated mean difference to be -32.6 (95% CI [-74.0713; 8.8713]; p = 0.1234) which indicates that ADIPOQ is not significantly decreased in patients with inactive SLE compared to healthy controls.

3.4.3 Ficolin-3 in systemic lupus erythematosus

A single study by Andersen, et al reported that FCN3 (measured in µg/ml using ELISA) is significantly increased in patients with SLE compared to healthy controls (mean difference = 20.5290; 95% CI [15.9401; 25.1179]; p < 0.0001).

3.4.4 Gelsolin in rheumatic heart disease

A single study by Argun, et al compared the levels of GSN in patients with RHD to healthy controls. The study measured GSN in µg/ml using ELISA. The mean difference was determined to be -124.73 (95% CI [-248.8378; -0.6222]; p = 0.0489). This suggests that GSN is significantly decreased in patients with RHD in comparison to healthy individuals.

3.4.5 Gelsolin in systemic lupus erythematosus

Two studies measured the level of GSN in patients with SLE and healthy controls. Both studies used ELISA and measurements were taken in µg/ml. The magnitude of effect was calculated to be -310.2682 (95% CI [-858.7314; 238.1950]; p = 0.2675; I^2 = 96%). This suggests high heterogeneity and

a non-statistically significant result. Therefore, GSN is decreased in SLE patients in comparison to controls however, not statistically significant.

3.4.5.1 Cases with a flare vs controls

A single study by Parra, et al calculated mean difference to be -112.29 (95% CI [-145.5296; -79.0504]; $p < 0.0001$), suggesting a significant decrease in GSN levels in SLE patients experiencing a flare-up in comparison to healthy controls.

3.4.5.2 Cases in remission vs controls

The mean difference was calculated to be -56.92 (95% CI [-84.5429; -29.2971]; $p < 0.0001$), indicating a significant decrease in SLE patients in remission in comparison to healthy controls, according to one study.

3.5 Narrative review of studies not included in the meta-analysis

3.5.1 Cross-sectional studies

Amongst the cross-sectional studies not amenable to meta-analysis, a single study by Mahieu, et al observed the levels of ADIPOQ in SLE patients. The study measured ADIPOQ using Luminex in µg/ml. The mean ADIPOQ level in patients was 11.8812 µg/ml with a standard deviation (SD) of 7.1975.

The remaining six studies looked at the levels of ADIPOQ in RA measured in µg/ml using ELISA. Borman, et al observed a mean ADIPOQ level of 16.08 µg/ml with a SD of 6.95. The study further found that there was no statistical difference in ADIPOQ levels between male and female patients ($p = 0.158$). Chen, et al observed a mean ADIPOQ level of 25.0 µg/ml (SD, 19.1). Gonzalez- Gay, et al observed a higher mean level of ADIPOQ in women with RA (21.595 µg/ml, CI [15.366; 30.349]) compared to men (9.31 µg/ml, CI [5.653; 15.335], $p = 0.008$). The patients in Targonska-Stepniak, et al 2010 had a mean ADIPOQ level of 15.2 µg/ml (SD, 9.4) with no statistical difference between males and females (11.4 vs 15.5 µg/ml). Targonska-Stepniak, et al conducted another study in 2022 which measured a mean ADIPOQ level of 10.7016 µg/ml (SD, 6.9871) in RA patients. The study additionally found that ADIPOQ levels negatively corresponded to BMI levels in patients ($p = 0.02$). In Giles, et al patients had a mean ADIPOQ level of 31.6487 µg/ml (SD, 17.2144).

3.5.2 Case-control studies

Sixteen case-control studies were not amenable to meta-analysis due to a lack of necessary and/or clear values being reported in their results. Therefore, the overall outcome of the studies is presented in a narrative.

A single case-control study by Catarino, et al studied the levels of FCN3 in RHD using ELISA. The study found that FCN3 was significantly downregulated in cases of RHD compared to healthy controls ($p < 0.0001$).

Two studies, utilising ELISA assays, examined the levels of ADIPOQ in SLE patients and healthy controls. Both studies (Chougule, et al and Vadacca, et al), observed no statistical difference between cases and controls ($p = 0.663$, $p = 0.63$ respectively).

Six studies evaluated levels of ADIPOQ in RA cases and controls. Four studies utilised ELISA and the remaining two used Luminex to measure ADIPOQ levels. Of the six, four concluded that there was no statistical difference in ADIPOQ levels between RA patients and healthy controls ($p = 0.16 – 0.332$). Two studies by Qian, et al and Sirenko, et al concluded that ADIPOQ was upregulated in RA cases ($p< 0.01$).

Two studies (Hein, et al and Plawecki, et al), utilizing ELISA assays, evaluated the levels of FCN3 in patients with SLE and healthy controls. Both studies concluded that FCN3 levels were significantly upregulated in SLE cases compared to healthy controls ($p= 0.0098$ and $p< 0.0001$).

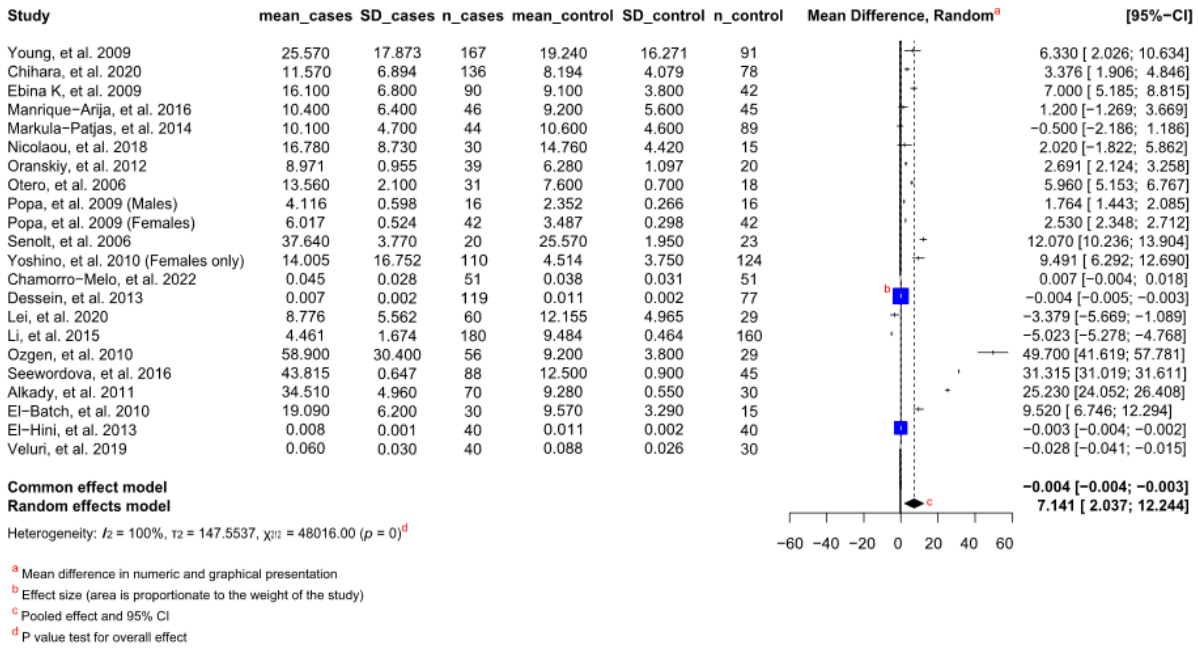
Four studies (Lee, et al; Mun, et al; Park, et al and Kang, et al) observed the levels of GSN in RA patients and controls. Three of the studies utilised ELISA whilst one used mass spectrometry to measure GSN levels. Two studies observed GSN levels to be downregulated in RA cases compared to healthy controls ($p< 0.05$ and $p< 0.01$) while the remaining 2 studies concluded that GSN was upregulated in cases ($p< 0.01$ and $p< 0.001$).

A single study by Yang, et al, utilising ELISA assays evaluated AZGP1 levels in SLE patients and healthy controls which was significantly upregulated in cases of SLE ($p< 0.001$).

Table 3. Meta-analysis of case-control studies, by subgroup, of the discriminatory power of biomarkers for autoimmune disease diagnosis

Protein	Disease/Subgroup	No. of studies	No. of participants	Pooled Mean Difference [95% CI]	I^2 Statistic (%)	p-value	Overall interpretation
ADIPOQ	**RA**	**21**	**2614**	**7.1407 [2.0373; 12.2440]**	**100.0**	**0.0061**	**↑ in cases. Significant**
	Severe RA	1	95	8.6000 [6.4612; 10.7388]	N/A	< 0.0001	↑ in severe cases. Significant
	Mild RA	1	79	4.8000 [2.4110; 7.1890]	N/A	< 0.0001	↑ in mild cases. Significant
	Active RA	3	149	14.1043 [-2.6316; 30.8402]	100.0	0.0986	↑ in active cases. Not significant
	Remission	3	141	5.3388 [-0.5476; 11.2252]	99.9	0.0755	↑ in cases in remission. Not significant
	SLE	**7**	**1103**	**3.6426 [1.7126; 5.5727]**	**93.5**	**0.0002**	**↑ in cases. Significant**
	Active SLE	1	54	-29.3000 [-69.2097; 10.6097]	N/A	0.1502	↓ in active cases. Not significant
	Inactive SLE	1	64	-32.6000 [-74.0713; 8.8713]	N/A	0.1234	↓ in inactive cases. Not significant
FCN3	**SLE**	**1**	**198**	**20.5290 [15.9401; 25.1179]**	**N/A**	**< 0.0001**	**↑ in cases. Significant**
GSN	**RHD**	**1**	**61**	**-124.7300 [-248.8378; -0.6222]**	**N/A**	**0.0489**	**↓ in cases. Significant**
	SLE	**2**	**230**	**-310.2682 [-858.7314; 238.1950]**	**96.0**	**0.2675**	**↓ in cases. Not significant**
	With flare	1	60	-112.2900 [-145.5296; -79.0504]	N/A	< 0.0001	↓ in cases with flare. Significant
	Under remission	1	136	-56.9200 [-84.5429; -29.2971]	N/A	< 0.0001	↓ in cases in remission. Significant

Figure 2. Forest plot of the association between adiponectin and rheumatoid arthritis



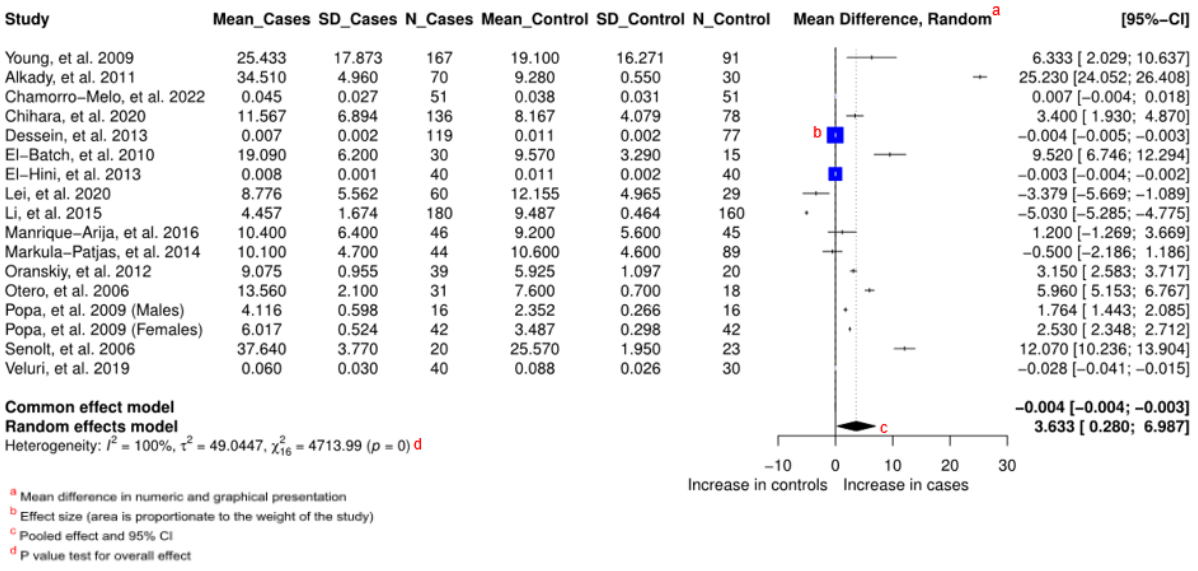
Study	mean_cases	SD_cases	n_cases	mean_control	SD_control	n_control	Mean Difference, Random[a]	[95%−CI]
Young, et al. 2009	25.570	17.873	167	19.240	16.271	91		6.330 [2.026; 10.634]
Chihara, et al. 2020	11.570	6.894	136	8.194	4.079	78		3.376 [1.906; 4.846]
Ebina K, et al. 2009	16.100	6.800	90	9.100	3.800	42		7.000 [5.185; 8.815]
Manrique−Arija, et al. 2016	10.400	6.400	46	9.200	5.600	45		1.200 [−1.269; 3.669]
Markula−Patjas, et al. 2014	10.100	4.700	44	10.600	4.600	89		−0.500 [−2.186; 1.186]
Nicolaou, et al. 2018	16.780	8.730	30	14.760	4.420	15		2.020 [−1.822; 5.862]
Oranskiy, et al. 2012	8.971	0.955	39	6.280	1.097	20		2.691 [2.124; 3.258]
Otero, et al. 2006	13.560	2.100	31	7.600	0.700	18		5.960 [5.153; 6.767]
Popa, et al. 2009 (Males)	4.116	0.598	16	2.352	0.266	16		1.764 [1.443; 2.085]
Popa, et al. 2009 (Females)	6.017	0.524	42	3.487	0.298	42		2.530 [2.348; 2.712]
Senolt, et al. 2006	37.640	3.770	20	25.570	1.950	23		12.070 [10.236; 13.904]
Yoshino, et al. 2010 (Females only)	14.005	16.752	110	4.514	3.750	124		9.491 [6.292; 12.690]
Chamorro−Melo, et al. 2022	0.045	0.028	51	0.038	0.031	51		0.007 [−0.004; 0.018]
Dessein, et al. 2013	0.007	0.002	119	0.011	0.002	77		−0.004 [−0.005; −0.003]
Lei, et al. 2020	8.776	5.562	60	12.155	4.965	29		−3.379 [−5.669; −1.089]
Li, et al. 2015	4.461	1.674	180	9.484	0.464	160		−5.023 [−5.278; −4.768]
Ozgen, et al. 2010	58.900	30.400	56	9.200	3.800	29		49.700 [41.619; 57.781]
Seewordova, et al. 2016	43.815	0.647	88	12.500	0.900	45		31.315 [31.019; 31.611]
Alkady, et al. 2011	34.510	4.960	70	9.280	0.550	30		25.230 [24.052; 26.408]
El−Batch, et al. 2010	19.090	6.200	30	9.570	3.290	15		9.520 [6.746; 12.294]
El−Hini, et al. 2013	0.008	0.001	40	0.011	0.002	40		−0.003 [−0.004; −0.002]
Veluri, et al. 2019	0.060	0.030	40	0.088	0.026	30		−0.028 [−0.041; −0.015]
Common effect model								**−0.004 [−0.004; −0.003]**
Random effects model								**7.141 [2.037; 12.244]**

Heterogeneity: I_2 = 100%, τ_2 = 147.5537, χ_{20} = 48016.00 (p = 0)[d]

−60 −40 −20 0 20 40 60

[a] Mean difference in numeric and graphical presentation
[b] Effect size (area is proportionate to the weight of the study)
[c] Pooled effect and 95% CI
[d] P value test for overall effect

Figure 3. Forest plot of the association between adiponectin and rheumatoid arthritis after the removal of outliers and high risk of bias studies



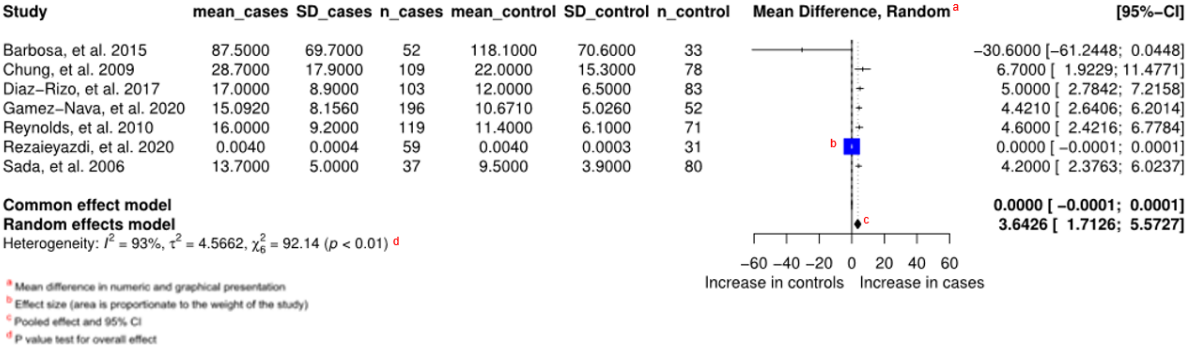
Study	Mean_Cases	SD_Cases	N_Cases	Mean_Control	SD_Control	N_Control	Mean Difference, Random[a]	[95%−CI]
Young, et al. 2009	25.433	17.873	167	19.100	16.271	91		6.333 [2.029; 10.637]
Alkady, et al. 2011	34.510	4.960	70	9.280	0.550	30		25.230 [24.052; 26.408]
Chamorro−Melo, et al. 2022	0.045	0.027	51	0.038	0.031	51		0.007 [−0.004; 0.018]
Chihara, et al. 2020	11.567	6.894	136	8.167	4.079	78		3.400 [1.930; 4.870]
Dessein, et al. 2013	0.007	0.002	119	0.011	0.002	77		−0.004 [−0.005; −0.003]
El−Batch, et al. 2010	19.090	6.200	30	9.570	3.290	15		9.520 [6.746; 12.294]
El−Hini, et al. 2013	0.008	0.001	40	0.011	0.002	40		−0.003 [−0.004; −0.002]
Lei, et al. 2020	8.776	5.562	60	12.155	4.965	29		−3.379 [−5.669; −1.089]
Li, et al. 2015	4.457	1.674	180	9.487	0.464	160		−5.030 [−5.285; −4.775]
Manrique−Arija, et al. 2016	10.400	6.400	46	9.200	5.600	45		1.200 [−1.269; 3.669]
Markula−Patjas, et al. 2014	10.100	4.700	44	10.600	4.600	89		−0.500 [−2.186; 1.186]
Oranskiy, et al. 2012	9.075	0.955	39	5.925	1.097	20		3.150 [2.583; 3.717]
Otero, et al. 2006	13.560	2.100	31	7.600	0.700	18		5.960 [5.153; 6.767]
Popa, et al. 2009 (Males)	4.116	0.598	16	2.352	0.266	16		1.764 [1.443; 2.085]
Popa, et al. 2009 (Females)	6.017	0.524	42	3.487	0.298	42		2.530 [2.348; 2.712]
Senolt, et al. 2006	37.640	3.770	20	25.570	1.950	23		12.070 [10.236; 13.904]
Veluri, et al. 2019	0.060	0.030	40	0.088	0.026	30		−0.028 [−0.041; −0.015]
Common effect model								**−0.004 [−0.004; −0.003]**
Random effects model								**3.633 [0.280; 6.987]**

Heterogeneity: I^2 = 100%, τ^2 = 49.0447, χ^2_{16} = 4713.99 (p = 0) [d]

−10 0 10 20 30
Increase in controls Increase in cases

[a] Mean difference in numeric and graphical presentation
[b] Effect size (area is proportionate to the weight of the study)
[c] Pooled effect and 95% CI
[d] P value test for overall effect

Figure 4. Forest plot of the association between adiponectin and systemic lupus erythematosus



Study	mean_cases	SD_cases	n_cases	mean_control	SD_control	n_control	Mean Difference, Random[a]	[95%−CI]
Barbosa, et al. 2015	87.5000	69.7000	52	118.1000	70.6000	33		−30.6000 [−61.2448; 0.0448]
Chung, et al. 2009	28.7000	17.9000	109	22.0000	15.3000	78		6.7000 [1.9229; 11.4771]
Diaz−Rizo, et al. 2017	17.0000	8.9000	103	12.0000	6.5000	83		5.0000 [2.7842; 7.2158]
Gamez−Nava, et al. 2020	15.0920	8.1560	196	10.6710	5.0260	52		4.4210 [2.6406; 6.2014]
Reynolds, et al. 2010	16.0000	9.2000	119	11.4000	6.1000	71		4.6000 [2.4216; 6.7784]
Rezaieyazdi, et al. 2020	0.0040	0.0004	59	0.0040	0.0003	31		0.0000 [−0.0001; 0.0001]
Sada, et al. 2006	13.7000	5.0000	37	9.5000	3.9000	80		4.2000 [2.3763; 6.0237]
Common effect model								**0.0000 [−0.0001; 0.0001]**
Random effects model								**3.6426 [1.7126; 5.5727]**

Heterogeneity: I^2 = 93%, τ^2 = 4.5662, χ^2_6 = 92.14 (p < 0.01) [d]

−60 −40 −20 0 20 40 60
Increase in controls Increase in cases

[a] Mean difference in numeric and graphical presentation
[b] Effect size (area is proportionate to the weight of the study)
[c] Pooled effect and 95% CI
[d] P value test for overall effect

CHAPTER 4 DISCUSSION

This systematic review and meta-analysis documents evidence for four in-silico predicted biomarkers in a selection of autoimmune diseases. The main findings were: (1) There is a significant increase in ADIPOQ in patients with RA (including both severe and mild cases of RA) as compared to healthy patients. (2) Adiponectin is significantly increased in cases of SLE compared to healthy controls. (3) Ficolin-3 is significantly increased in cases of SLE compared to healthy controls. (4) Gelsolin is significantly decreased in cases of RHD as well as in cases of SLE with a flare and under remission compared to healthy controls. (5) Ficolin-3 is significantly decreased in RHD patients compared to healthy patients. (6) Ficolin-3 and AZGP1 were both significantly increased in SLE cases compared to healthy controls.

4.1 Review of studies included in the meta-analysis

4.1.1 Adiponectin in rheumatoid arthritis

When observing the level of ADIPOQ in patients with RA, there was a clear significant increase in ADIPOQ amongst patients with RA compared to healthy controls (Figure 2). Despite the removal of outliers and studies with a high risk of bias, the result remained the same and the heterogeneity remained high. Ozgen, et al had no observed difference in study design to justify their noticeably high results. Seewordova, et al, however, consisted of cases with a comorbidity of osteoporosis which may explain the high levels of ADIPOQ. Osteoporosis is an inflammation-induced disease characterised by low bone mass and increased bone fragility (107). When referring to Figure 2, the studies are grouped according to the income status of the country in which they were conducted; the studies are ordered from high to low income and no discernible trends were observed.

The subgroup analyses comparing severe and mild cases of RA to controls consisted of a single study which preventing generalisable conclusions. The study concluded that ADIPOQ is increased in both groups in comparison to controls, with a higher mean concentration in severe cases than mild cases. The latter is of benefit, as it shows the potential of ADIPOQ as a suitable biomarker, such that it is able to delineate across disease progression. However, these conclusions should be taken with caution, requiring further validation with an increased population size to confirm the validity of the result.

Out of all the cross-sectional studies observing ADIPOQ levels in RA patients, these studies, specifically those with a low risk of bias are of value, as they will provide future researchers evaluating levels of ADIPOQ of similar regions, with a baseline titre or an expected range for what the concentration levels of ADIPOQ should be within cases of RA.

Of the eight case-control studies, six studies were in agreement that there was no significant difference, while the remaining studies were congruent with the meta-analysis.

The subgroup analyses comparing active and remission cases of RA to controls had an outlier which when removed increased the magnitude of effect and made it statistically significant. Veluri, et al was the only study in the subgroup analyses that had a study population that was from India. The other 2 studies had study populations from Egypt. This may have contributed to the outlying results from Veluri, et al.

4.1.2 Adiponectin in systemic lupus erythematosus

Adiponectin is significantly upregulated in SLE patients in comparison to healthy controls. The removal of Barbosa, et al as an outlier had no effect on the overall result. Despite this observation, Barbosa, et al had conflicting results with other studies, showing a decrease in cases in comparison to controls (Figure 4). The study by Rezaieyazdi, et al had a much smaller magnitude of effect compared to the other studies. These differing results may be attributed to the method (ELISA assays) utilised to measure ADIPOQ concentrations as well as the population tested, which were on average, ten years older than the participants of the other studies. Furthermore, only one study separated the case population in active SLE and inactive SLE cases thus, no discernible conclusion can be made based on ADIPOQ levels in comparison to controls.

For the studies in the narrative review portion, when examining ADIPOQ levels in SLE patients, both studies had comparable results which conflicted the meta-analysis. Additionally, Chougule, et al furthermore had a high risk of bias and thus affecting the validity of the conflicting data.

It is clear from these results, that in both autoimmune diseases, that ADIPOQ is significantly increased in expression in comparison to the healthy population. Therefore, we suggest, the utility of ADIPOQ as a potential biomarker for RHD will not be feasible however, it could be used as an additional marker for autoimmune disease in general. This in fact, could still be beneficial in decreasing the burden of healthcare systems, in which only patients tested for high levels of ADIPOQ should be referred for further workup including echocardiography (RHD), immunologic assays (SLE) and imaging (RA).

4.1.3 Ficolin-3

There were two studies observing FCN3 levels in healthy controls and SLE patients, one of which was a case-control study. Both studies concluded that FCN3 was upregulated in SLE patients compared to healthy individuals. Furthermore, there was one study provided evidence that FCN3 was downregulated in RHD patients. From these conflicting results, we suggest that more studies be conducted on both SLE and RHD populations, as it will provide clarity as to whether or not, FCN3 may still be a suitable biomarker for RHD.

4.1.4 Gelsolin

Only a single study measured GSN levels in RHD patients and healthy controls, suggesting that GSN was significantly downregulated in RHD patients. However, all the RHD patients in the study had a comorbidity of either arthritis or Sydenham's chorea. These diseases involve inflammation and other unknown mechanisms which may have contributed to the levels of GSN in the patients.

When referring to GSN in SLE patients, the levels were decreased in cases in comparison to controls, albeit, not statistically significant. Interestingly, all four case-control studies that examined GSN in RA, were conducted in South Korea within the span of 5 years (2014 – 2019), having minimal difference between study populations however, still produced contradictory results in GSN levels. We conclude that GSN as a biomarker for autoimmune disease or specifically RHD is still unclear, and more studies are required.

4.2 Narrative review of studies not included in the meta-analysis

4.2.1 Cross-sectional studies

Of all the cross-sectional studies observing ADIPOQ levels in RA patients, Giles, et al was the only study to consist of more male patients than female (57%). The rest of the studies had a much larger proportion of females compared with males in the study population. Adiponectin levels have been observed to differ between males and females (108). This may account for the much larger mean ADIPOQ level observed in Giles, et al compared to the other studies. Studies excluded due to a high risk of bias included Borman, et al, Targonska-Stepniak, et al 2010, Targonska-Stepniak, et al 2022 and Giles, et al.

4.2.2 Case-control studies

Catarino, et al., measured FCN3 in RHD patients, as there are no other studies examining FCN3 in RHD, this result cannot be generalised despite its statistical significance.

When examining ADIPOQ levels in SLE patients, despite the comparable results between the two studies, these findings cannot be generalised as there are not enough studies present to make a substantial conclusion. Additionally, these results conflict with the meta-analysis that determined ADIPOQ to be significantly increased in SLE patients. Chougule, et al furthermore has indicated a high risk of bias affecting the validity of its results.

When examining ADIPOQ levels in RA patients, of the six studies in agreement that there was no significant difference, one of which had a high risk of bias. As for the two studies that showed an upregulation of ADIPOQ, which coincides with the meta-analysis, although, deemed as having a high risk of bias. Additionally, one of the studies, Sirenko, et al consisted of cases and controls that has a comorbidity of hypertension which may have affected the levels of ADIPOQ in the study population.

When examining FCN3 levels in patients with SLE, despite both of the studies having a high risk of bias, these results were concurrent with the study completed by Andersen, et al as discussed above.

When examining GSN levels in RA patients, one of the four studies consisted of controls suffering from osteoarthritis, known to alter the levels of GSN in the body (109). Interestingly, all four studies were conducted in South Korea within the span of 5 years (2014 – 2019), having minimal difference between study populations however, still producing contradictory results.

Despite the statistical significance of many of these results, there are many discrepancies within the data and contradictions between studies, therefore there are gaps in the research. Future research is required to fill these gaps in knowledge as the current research has proven these biomarkers to be of great potential in the diagnosis of autoimmune diseases.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

One of the main strengths of this review, was the stringent methodology incorporated into the systematic review, including a search of multiple databases. Additionally, throughout the entire review process, two independent reviewers conducted the screening and data extraction processes to mitigate any selection bias. The same two independent reviewers conducted the risk of bias assessment to understand the quality of the studies included whilst also, allowing for comparisons to be made. Any high risk of bias in studies was taken into account during the analysis of results. Three independent reviewers assisted in obtaining the correct values and the standardized conversions before performing the statistical analysis, avoiding calculation errors.

One of the main limitations of the review is the dearth of studies conducted on the included putative biomarkers, limiting us to provide conclusions on only four of 13 proteins. Another challenge was encountered during the statistical analysis, as the data had to be transformed from medians and interquartile ranges to mean scores and standard deviations. There was quite a few of the studies that were not amenable to the meta-analysis, and thus included in the narrative review portion mainly due to missing data and results from figures and tables were difficult to extrapolate.

CHAPTER 5 CONCLUSION

This review documented significantly upregulated or downregulated proteins in autoimmune diseases which, with further validation, could be useful as early detection markers of the respective diseases. As for their usefulness in specifically identifying a case of RHD from amongst other diseases, remains to be evaluated. FCN3 and GSN despite being also associated with SLE and RA, may still be of significance as a marker for RHD specifically, depending on whether it is downregulated in RHD or

upregulated in RHD respectively, whereas ADIPOQ could be used as a marker for autoimmune disease. These proteins along with the nine proteins not previously identified, should be further evaluated in terms of their discriminatory power for the development of a point-of-care diagnostic test. A diagnostic test will enable early screening and diagnosis, capable of referring patients at risk for disease for further workup, thus alleviating the burden on healthcare facilities in resource poor areas.

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Note: the Vancouver referencing format has been used in this review.

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APPENDICES

Appendix A: Search strategy

Subject	MeSH terms
Rheumatic heart disease	"Rheumatic heart disease" OR "RHD"
Systemic lupus erythematosus	"Systemic lupus erythematosus" OR "SLE" OR "lupus" OR "disseminated lupus erythematosus"
Rheumatoid arthritis	"Rheumatoid arthritis" OR "RA" OR "rheumatism" OR "atrophic arthritis"
Adiponectin	"Adiponectin" OR "GBP-28" OR "APM-1" OR "ADIPOQ" OR "ACDC" OR "Acrp-30" OR "gelatin-binding protein"
Complement C7	"Complement C7" OR "complement component C7" OR "C7"
Quiescin sulfhydryl oxidase 1	"Quiescin sulfhydryl oxidase 1" OR "QSOX1"
Insulin like growth factor binding protein complex acid labile subunit	"Insulin like growth factor binding protein complex acid labile subunit" OR "IGFALS"
Pregnancy zone protein	"Pregnancy zone protein" OR "PZP"
Glycosylphosphatidylinositol specific phospholipase D1	"Glycosylphosphatidylinositol specific phospholipase D1" OR "GPLD1"
Fibulin 1	"Fibulin 1" OR "FBLN1"
Alpha-2-glycoprotein 1	"Alpha-2-glycoprotein 1" OR "AZGP1" OR "zinc-binding" OR "Zn-alpha-2-glycoprotein"
Gelsolin	"Gelsolin" OR "GSN"
Ficolin-3	"Ficolin-3" OR "FCN3" OR "Collagen/fibrinogen domain-containing lectin 3 p35" OR "Collagen/fibrinogen domain-containing protein 3" OR "hakata antigen" OR "HAKA1" OR "FCNH"
C-Reactive protein	"C-Reactive protein" OR "CRP"
Olfactomedin 1	"Olfactomedin 1" OR "OLFM1" OR "Noelin" OR "Neuronal olfactomedin-related ER localized protein" OR "NOE1"
Protein disulfide-isomerase	"Protein disulfide-isomerase" OR "P4HB"
Filamin B	"Filamin B" OR "FLNB"
Case-control study	"Case-control study" OR "retrospective study"
Cross-sectional study	"Cross-sectional study" OR "cross-sectional analysis" OR "transverse study" OR "prevalence study"

Appendix B: Characteristics of excluded studies

Study ID	Title	Reason for exclusion
Alcalay, et al. 1980	Hereditary-deficiency in complement C7 and platelet-aggregation disorders associated with rheumatoid-arthritis - one case	Wrong study design
Alcalay, et al. 1981	C7 deficiency, abnormal platelet-aggregation, and rheumatoid-arthritis	Wrong lab method
Aletaha, et al. 2006	The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey	Wrong biomarker
Ali, et al. 2021	Inflammatory and bone biomarkers/composites as a predictive tool for clinical characteristics of rheumatoid arthritis patients	Wrong biomarker
Aprahamian, et al. 2009	The Peroxisome Proliferator-Activated Receptor gamma Agonist Rosiglitazone Ameliorates Murine Lupus by Induction of Adiponectin	Wrong population
Bach, et al. 2020	A Neutrophil Activation Biomarker Panel in Prognosis and Monitoring of Patients With Rheumatoid Arthritis	Wrong Biomarker
Barbosa, et al. 2012	Possible role of adipokines in systemic lupus erythematosus and rheumatoid arthritis	Wrong study design
Barturen, et al. 2021	Integrative Analysis Reveals a Molecular Stratification of Systemic Autoimmune Diseases	Wrong Biomarker
Beerelli, et al. 2012	Lupus-like syndrome in C7 deficiency	Full text not found
Biró, et al. 2007	Activated complement components and complement activator molecules on the surface of cell-derived microparticles in patients with rheumatoid arthritis and healthy individuals	Wrong Biomarker

Boyer, et al. 2012	Link between traditional cardiovascular risk factors and inflammation in patients with early arthritis: Results from a French multicenter cohort	Wrong Biomarker
Cansu, et al. 2011	Disease-Modifying Antirheumatic Drugs Increase Serum Adiponectin Levels in Patients With Rheumatoid Arthritis	Wrong study design
Carbone, et al. 2020	Serum adiponectin levels are associated with presence of carotid plaque in women with systemic lupus erythematosus	Wrong study design
Chamorro-Melo, et al. 2020	ROC analysis of adipokines (adiponectin, resistin, adipsin, vaspin and leptin) in patients with early rheumatoid arthritis	Updated version found
Chamorro-Melo, et al. 2022	Evaluation of the adipokine profile (adiponectin, resistin, adipsin, vaspin, and leptin) in patients with early rheumatoid arthritis and its correlation with disease activity.	Full text not found
Chaparro-Sanabria, et al. 2018	Relationship between adiponectin levels and disease activity and functional index measures in early rheumatoid arthritis patients	Full text not found
Chaparro-Sanabria, et al. 2019	Association of adipokines with rheumatic disease activity indexes and periodontal disease in patients with early rheumatoid arthritis and their first-degree relatives	Wrong study design
Chen, et al. 2013	Adiponectin: A biomarker for rheumatoid arthritis?	Wrong study design
Chen, et al. 2021	No Causal Association Between Adiponectin and the Risk of Rheumatoid Arthritis: A Mendelian Randomization Study	No biomarker measured
Choi, et al. 2005	Lipid profiles among US elderly with untreated rheumatoid arthritis - The Third National Health and Nutrition Examination Survey	Wrong Biomarker

Copotoiu, et al. 2012	Adiponectin, leptin, resistin - players in driving the rheumatoid arthritis activity	Full text not found
Dabadghao, et al. 2018	A clinical study of acute-phase reactants and immunological markers in patients of chronic inflammatory arthritis in a tertiary care setting	Wrong biomarker
Dan, et al. 2021	Circulating adiponectin levels and systemic lupus erythematosus: a two-sample Mendelian randomization study	No biomarker measured
Dessein, et al. 2014	Adiponectin and Atherosclerosis in Rheumatoid Arthritis	Wrong study design
Diaz-Rizo, et al. 2014	Macrophage migration inhibitory factor, resistin, leptin, adiponectin and clinical variables in systemic lupus erythematosus	Full text not found
do Prado, et al. 2022	Selenium nutritional status and its association with SLEDAI-2K, HOMA-IR and lipid profile in Juvenile Systemic Lupus Erythematosus patients.	Wrong biomarker
Ehling, et al. 2003	Adipocytokine apM-1 (adiponectin) is upregulated in rheumatoid arthritis synovium and modulates cytokine production in synovial fibroblasts	Full text not found
Eidet, et al. 2015	A Low Adiponectin Level in Rheumatoid Arthritis Is Associated with Coronary Artery Disease	Full text not found
Eidet, et al. 2015	Serum level of adiponectin in rheumatoid arthritis (RA) is associated with coronary artery disease	Full text not found
Eilertsen, et al. 2011	Increased levels of BAFF in patients with systemic lupus erythematosus are associated with acute-phase reactants, independent of BAFF genetics: a case-control study.	Wrong biomarker
Esawy, et al. 2020	Plasma gelsolin levels in patients with psoriatic arthritis: a possible novel marker	Wrong population

Foeldvari, et al. 2022	Differences Sustained Between Diffuse and Limited Forms of Juvenile Systemic Sclerosis in an Expanded International Cohort	No biomarker measured
Frade-Sosa, et al. 2020	A comparative study on clinical and serological characteristics between patients with rhupus and those with systemic lupus erythematosus and rheumatoid arthritis	No biomarker measured
Frommer, et al. 2011	Adiponectin isoforms differentially affect gene expression of rheumatoid arthritis synovial fibroblasts	Wrong study design
Frommer, et al. 2012	Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis?	Wrong study design
Galiutina, et al. 2018	Serum leptin and adiponectin levels in rheumatoid arthritis patients, their association with inflammatory process	Wrong lab method
Geiger, et al. 1975	Study of complement components C3, C5, C6, C7, C8 and C9 in chronic membranoproliferative glomerulonephritis, systemic lupus-erythematosus, poststreptococcal nephritis, idiopathic nephrotic syndrome and anaphylactoid purpura	Wrong study design
George, et al. 2017	Impact of Obesity and Adiposity on Inflammatory Markers in Patients With Rheumatoid Arthritis	Wrong biomarker
Georgiadis, et al. 2006	Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: Effect of early treatment - A prospective, controlled study	Wrong study design
Ghamrawy, et al. 2020	How accurate is the diagnosis of rheumatic fever in egypt? Data from the national rheumatic heart disease prevention and control program (2006-2018)	Wrong biomarker
Gilliam, et al. 2008	Measurement of biomarkers in juvenile idiopathic arthritis patients and their significant association with disease severity: A comparative study	Wrong biomarker

Gonzalez-Gay, et al. 2008	High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis	Wrong study design
Gorczyca, et al. 2017	The profile of polyunsaturated fatty acids in juvenile idiopathic arthritis and association with disease activity	Wrong biomarker
Gossec, et al. 2018	Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an analysis of 967 patients from two databases of early and established rheumatoid arthritis patients	No biomarker measured
Häupl, et al. 2008	Interaction between rheumatoid arthritis and pregnancy: correlation of molecular data with clinical disease activity measures.	Wrong biomarker
Hebert, et al. 2003	Management of lupus nephropathy (vol 93, pg c7, 2003)	Wrong study design
Hu, et al. 2016	Gelsolin deposits in renal tissues of the patients with lupus nephritis	Wrong study design
Idriss, et al. 2020	Is there a feasible link between vitamin d receptor genotypic and allelic frequencies with analytical biomarkers of rheumatoid arthritis disease?	Wrong biomarker
Jonsson, et al. 1995	Prospective analysis of C1 dissociation and complement activation in patients with systemic lupus erythematosus	Wrong biomarker
Joob, et al. 2019	Adiponectin and rheumatoid arthritis	Full text not found
Juda, et al. 2020	Adiponectin as anti-inflammatory and pro-inflammatory indicator among type 2 diabetes mellitus and rheumatoid arthritis in Iraqi population	Full text not found

Jung, et al. 2013	Possible predictive value of correlation between synovial angiogenesis and serum level of adiponectin in patients with rheumatoid arthritis	Full text not found
Kang, et al. 2013	The relationship between serum leptin: adiponectin ratio, insulin resistance, and carotid atherosclerosis in patients with rheumatoid arthritis	Full text not found
Kang, et al. 2014	Urinary proteome profile predictive of disease activity in rheumatoid arthritis	Wrong study design
Karpuz, et al. 2017	Can whole-blood parameters be used in follow-up of children with rheumatic valvular heart disease?	Wrong biomarker
Klein-Wieringa, et al. 2011	Adiponectin is a predictor for radiographic progression in early RA patients, independently of anti-CCP antibodies	Full text not found
Klein-Wieringa, et al. 2014	Are Baseline High Molecular Weight Adiponectin Levels Associated with Radiographic Progression in Rheumatoid Arthritis and Osteoarthritis?	Wrong study design
Kontny, et al. 2013	Multimeric adiponectin isoforms in rheumatoid arthritis: local and systemic effects	No biomarker measured
Krumbholz, et al. 2014	Adiponectin: modulation of bone remodelling in rheumatoid arthritis	No biomarker measured
Laczna, et al. 2022	Adiponectin Is a Component of the Inflammatory Cascade in Rheumatoid Arthritis	Wrong study design
Landolt-Marticorena, et al. 2013	Fluctuations In sVCAM-1 and Adiponectin Mirror Fluctuations In Disease Activity In Lupus, But Cannot Be Use To Accurately Predict Impending Changes In Disease State	Wrong study design

Laurberg, et al. 2009	Plasma Adiponectin in Patients with Active, Early, and Chronic Rheumatoid Arthritis Who Are Steroid- and Disease-Modifying Antirheumatic Drug-Naive Compared with Patients with Osteoarthritis and Controls	Wrong lab method
Lee, et al. 2018	Potential therapeutic antibodies targeting specific adiponectin isoforms in rheumatoid arthritis	Wrong study design
Lee, et al. 2020	Arthritis, Sleep Health, and Systemic Inflammation in Older Men	Wrong biomarker
Li, et al. 2022	Predictors of improvement in disease activity in first hospitalized patients with systemic lupus erythematosus: a multicenter retrospective study of a Chinese cohort.	Wrong biomarker
Liu, et al. 2015	Multifaceted roles of adiponectin in rheumatoid arthritis	Wrong study design
Liu, et al. 2021	Combining Calcitonin and Procalcitonin and Rheumatoid Arthritis-Related Biomarkers Improve Diagnostic Outcomes in Early Rheumatoid Arthritis	Wrong biomarker
Maese, et al. 2012	Management of rheumatoid arthritis in Spain (emAR II). Clinical characteristics of the patients	Wrong biomarker
Mahieu, et al. 2018	Serum adipokine levels and associations with patient-reported fatigue in systemic lupus erythematosus	Wrong study design
Masi, et al. 2013	Serum acute phase protein and inflammatory cytokine network correlations: Comparison of a pre-rheumatoid arthritis and non-rheumatoid arthritis community cohort	Wrong biomarker
Masi, et al. 2017	Preclinical biomarker associations with both incident rheumatoid arthritis and its subsequent mortality: Sex effects in a 41-year, community-based, case-control cohort study	Wrong biomarker
Mc Ardle, et al. 2022	Identification and Evaluation of Serum Protein Biomarkers That Differentiate Psoriatic Arthritis From Rheumatoid Arthritis	Wrong biomarker

Mercurio, et al. 2019	Inflammatory, serological and vascular determinants of cardiovascular disease in systemic lupus erythematosus patients	Wrong biomarker
Meyer, et al. 2013	Serum level of adiponectin is a surrogate independent biomarker of radiographic disease progression in early rheumatoid arthritis: results from the ESPOIR cohort	Wrong study design
Misra, et al. 2018	Association of Angiogenic and Inflammatory Markers with Power Doppler Ultrasound Vascularity Grade and DAS28-CRP in Early Rheumatoid Arthritis: A Comparative Analysis	Wrong biomarker
Moreno-Torres, et al. 2022	Usefulness of the hemogram as a measure of clinical and serological activity in systemic lupus erythematosus	No biomarker measured
Müller-Ladner, et al. 2009	The multifaceted role of adiponectin in inflammatory joint disease	Wrong study design
Naz, et al. 2013	Juvenile rheumatoid arthritis	Wrong biomarker
Neumann, et al. 2014	Adiponectin as Target in Rheumatoid Arthritis	Foreign language
Nilsson, et al. 2008	Different regulation of visfatin and adiponectin in rheumatoid arthritis	Full text not found
Osborn, et al. 2008	Decreased levels of the gelsolin plasma isoform in patients with rheumatoid arthritis	Wrong lab method
Parra, et al. 2015	Proteome analyses of HDL particles allows to identify biomarkers of disease activity in SLE patients: gelsolin, indian hedgehog protein and S100A8	Full text not found
Popescu, et al. 2012	Inhibitory Autoantibodies to Protein Disulfide Isomerase From Systemic Lupus Erythematosus Patients Are Prothrombotic	Wrong biomarker

Qu, et al. 2021	Immunoprofiling of active and inactive systemic juvenile idiopathic arthritis reveals distinct biomarkers: a single-center study	Wrong biomarker
Ramos-Casallas, et al. 2022	Adipokine profile on joint and periodontal conditions in first-degree relatives of patients with rheumatoid arthritis.	Wrong population
Ristić, et al. 2021	Impact of disease activity on impaired glucose metabolism in patients with rheumatoid arthritis	Wrong biomarker
Rodrigues, et al. 2021	Biomarkers of lipid metabolism in patients with juvenile idiopathic arthritis: relationship with disease subtype and inflammatory activity	Wrong biomarker
Rovin, et al. 2005	Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus	No biomarker measured
Salie, et al. 2022	Data-independent acquisition mass spectrometry in severe rheumatic heart disease (RHD) identifies a proteomic signature showing ongoing inflammation and effectively classifying RHD cases	Bias
Salma, et al. 2020	Rheumatoid arthritis: Seropositivity versus seronegativity; a comparative cross-sectional study arising from Moroccan context	Wrong biomarker
Santamaría-Alza, et al. 2018	Systemic lupus erythematosus, gender differences in Colombian patients	No biomarker measured
Schmalz, et al. 2020	Oral health-related quality of life in different rheumatic diseases.	Wrong biomarker
Segurado, et al. 1992	Combined total deficiency of C7 and C4B with systemic lupus erythematosus (SLE)	Wrong study design

Sellam, et al. 2013	Serum level of total adiponectin independently predicts rapid radiographic disease progression in early rheumatoid arthritis: a cohort study.	Wrong study design
Sellam, et al. 2014	Response to 'Serum level of adiponectin is a surrogate independent biomarker of radiographic disease progression in early rheumatoid arthritis: results from the ESPOIR cohort' - authors' reply	Wrong study design
Shen, et al. 2013	Association of disease activity and anti-rheumatic treatment in juvenile idiopathic arthritis with serum lipid profiles: A prospective study	Wrong biomarker
Sincer, et al. 2015	Association between serum total antioxidant status and flow-mediated dilation in patients with systemic lupus erythematosus: An observational study	Wrong biomarker
Sirenko, et al. 2016	The adiponectin level in hypertensive females with rheumatoid arthritis and its relationship with subclinical atherosclerosis	Full text not found
Sirenko, et al. 2018	Adiponectin level, insulin resistance, endothelial dysfunction in females with rheumatoid arthritis and comorbid hypertension	Full text not found
Sirenko, et al. 2018	Endothelial function, insulin resistance, adiponectin level in hypertensive females with rheumatoid arthritis and renal dysfunction	Full text not found
Sirenko, et al. 2018	Carotid atherosclerosis in females with rheumatoid arthritis: relationship with the adiponectin level, insulin resistance, endothelial function	Full text not found
Sirenko, et al. 2018	Insulin resistance, adiponectin level, endothelial function in rheumatoid arthritis females with heart failure with preserved ejection fraction	Full text not found

Smith, et al. 2017	Do classic blood biomarkers of JSLE identify active lupus nephritis? Evidence from the UK JSLE Cohort Study	Wrong biomarker
Szumilas, et al. 2020	Role of Adiponectin in the Pathogenesis of Rheumatoid Arthritis	Wrong study design
Tanaka, et al. 2008	Elevated serum leptin and adiponectin levels, but decreased resistin level in systemic lupus erythematosus	Full text not found
Tikly, et al. 2003	A longitudinal study of rheumatoid arthritis in South Africans.	Wrong biomarker
Toussirot, et al. 2014	Response to 'Serum level of adiponectin is a surrogate independent biomarker of radiographic disease progression in early rheumatoid arthritis: results from the ESPOIR cohort'-authors' reply	Wrong study design
Tunc, et al. 2006	The relevance of adiponectin with insulin resistance and disease activity in rheumatoid arthritis patients	Full text not found
Ucieklak, et al. 2013	H-ficolin (ficolin-3) concentrations and FCN3 gene poly- morphism in patients with lupus nephritis and primary glomerulonephritides	Wrong population
Vasileiadis, et al. 2020	Plasma adiponectin associates with clinical markers of disease activity and circulating chemokines in subjects with untreated early rheumatoid arthritis	No biomarker measured
Vazquez-Villegas, et al. 2021	Functional disability is related to serum chemerin levels in rheumatoid arthritis.	Wrong study design
Wang, et al. 2020	Identifying Vulnerable Plaque in Rheumatoid Arthritis Using Novel Microbubble Contrast-Enhanced Carotid Ultrasonography and Serum Biomarkers	Wrong biomarker

Wang, et al. 2021	Adiponectin induces synovial angiogenesis in rheumatoid arthritis through metabolic remodeling	No biomarker measured
Xibille, et al. 2013	Leptin and adiponectin serum levels as predictors of treatment response in patients with rheumatoid arthritis	Wrong study design
Xibille-Friedmann, et al. 2015	Leptin and adiponectin as predictors of disease activity in rheumatoid arthritis	Wrong study design
Xie, et al. 2022	A new perspective: Fat tissue and adipokines in rheumatic heart valves.	Wrong lab method
Yang, et al. 2015	Generation of a monoclonal antibody against adiponectin isoforms (HMW/MMW) for a therapeutic antibody against rheumatoid arthritis	Wrong study design
Yang, et al. 2018	Proteomic analysis of plasma from rheumatoid arthritis patients with mild cognitive impairment	Wrong biomarker
Ye, et al. 2022	Insulin resistance and adverse lipid profile in untreated very early rheumatoid arthritis patients: A single-center, cross-sectional study in China	Wrong biomarker
Yilmaz-Oner, et al. 2015	Biomarkers in remission according to different criteria in patients with rheumatoid arthritis	Wrong biomarker
Yokogawa, et al. 2020	A Proposal to Standardize Low Disease Activity Criteria in Rheumatoid Arthritis Based on the Outcome Measures in Rheumatology Minimal Disease Activity Definition	No biomarker measured
Yu, et al. 2018	Association between inflammation and systolic blood pressure in RA compared to patients without RA	Wrong biomarker

Zhang, et al. 2012	Discovery of serum protein biomarkers in rheumatoid arthritis using MALDI-TOF-MS combined with magnetic beads	Wrong biomarker
Zhang, et al. 2020	Elevated adiponectin predicts the development of rheumatoid arthritis in subjects with obesity	Wrong study design
Zhang, et al. 2021	Adiponectin Associates with Rheumatoid Arthritis Risk in Overweight and Obesity Independently of Other Adipokines	Wrong study design
Zhou, et al. 2016	Exploration of the serum metabolite signature in patients with rheumatoid arthritis using gas chromatography–mass spectrometry	Wrong biomarker
Zou, et al. 2022	Association Between Metabolic Dysfunction-Associated Fatty Liver Disease and Cardiovascular Risk in Patients With Rheumatoid Arthritis: A Cross-Sectional Study of Chinese Cohort	Wrong biomarker

Appendix C: Data extraction form

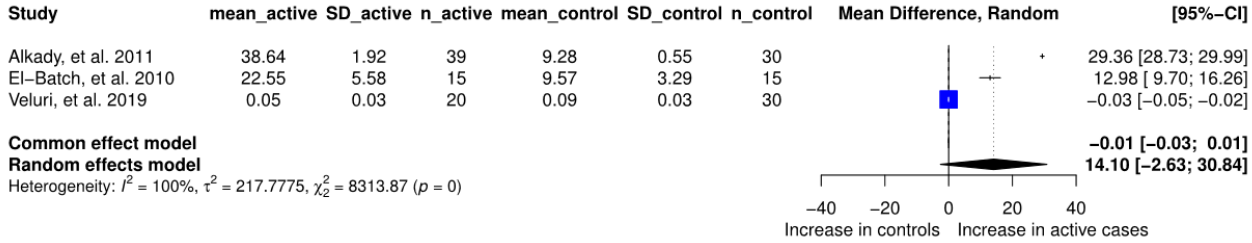
Review title	**Biomarkers for autoimmune disease diagnosis in the public health sector: A Systematic Review and Meta-Analysis**
Study ID (Authors and Year)	
Journal	
Publication type (e.g. Journal article, review)	
Study design	C/S □ C/C □
Disease studied	SLE □ RHD □ RA □
Classification used for disease	
Location	
Income status of country	HIC □ UMIC □ LMIC □ LIC □
Biomarker studied	ADIPOQ □ C7 □ QSOX1 □ PZP □ etc
Laboratory method	Mass spectrometry □ ELISA □ Luminex □ RT-PCR □
Specific laboratory method used (e.g. Sandwich ELISA)	
Include?	Yes □ No □
Reason for exclusion	
Study population (Sex)	
Average age of participants (Years)	
Average BMI of participants (kg/m²)	
Comorbidities in cases (e.g. Hypertension)	
Comorbidities in controls	
Total number of participants	
Control (N)	
Control (µg/ml)	
Median	
Minimum	
25%	
75%	
Maximum	
Mean	
SD	
Cases (N)	
Cases (µg/ml)	
Median	
Minimum	
25%	
75%	
Maximum	
Mean	
SD	
Sub-categories (e.g. patients with active RA, patients with inactive RA)	
Sub-categories (µg/ml)	
Comment	
Date of extraction (dd/mm/yyyy)	
Name of person extracting data	

Appendix D: Risk of Bias tool

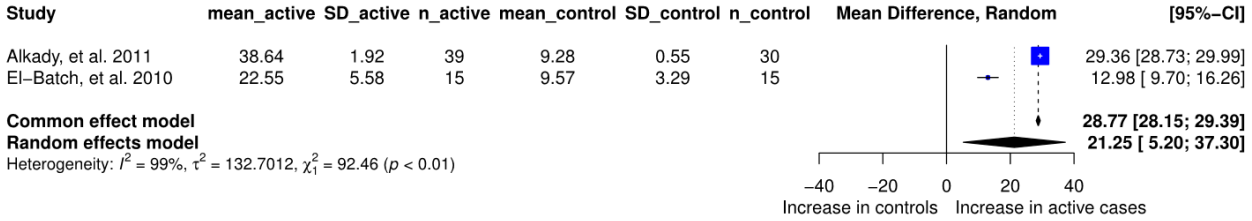
Review Title	**Biomarkers for autoimmune disease diagnosis in the public health sector: A Systematic Review and Meta-Analysis**
Study ID (Authors and Year)	
Journal	
Was the primary aim of the study to validate a biomarker for disease diagnosis?	Yes □ No □
Did the study detail a scientifically valid reason for choosing the given biomarker for investigation?	Yes □ No □
Was the biomarker measured using an appropriate method?	Yes □ No □
Has an assessment of the effect of likely confounding factors (e.g. age, gender, smoking status, and being on symptomatic PD treatment) on the measurement of the biomarker been made?	Yes □ No □
Has a valid and reliable criterion (e.g. clinical rating scale) been used?	Yes □ No □
Was a power calculation undertaken to determine the required number of participants?	Yes □ No □
If a power calculation was undertaken, was the number of participants included appropriate?	Yes □ No □ N/A □
Was measurement of the biomarker blind to participant characteristics?	Yes □ No □
Were cases unselected/unbiased (exclusion criteria present)?	Yes □ No □
Definition of controls (no history of disease)	Yes □ No □ N/A □
Comparability of cases and controls (the study controls for possible confounding factor/s)	Yes □ No □ N/A □
Were associations between the biomarker and clinical measures of disease severity examined for using appropriate statistical modelling (e.g. linear mixed modelling) with adjustment for confounding factors, rather than simply correlation analysis?	Yes □ No □
Were results of statistical analyses reported in sufficient detail to allow the inclusion of the study results in a meta-analysis?	Yes □ No □
Total score (out of 13)	
Risk Scale	1 – 5 : High risk of bias 6 – 10 : Moderate risk of bias 11 – 13 : Low risk of bias

Appendix E: Forest plots

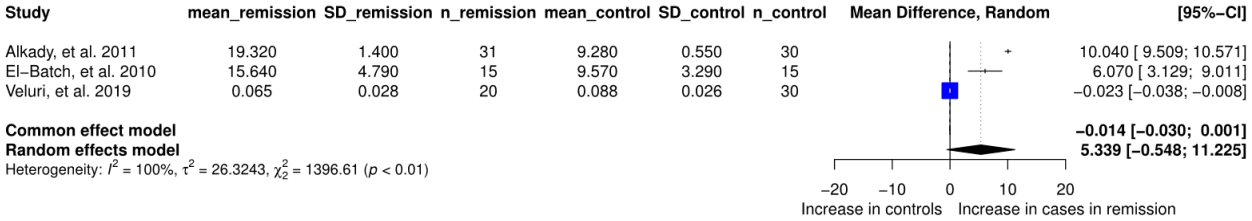
Forest plot of the association between adiponectin and active cases of rheumatoid arthritis



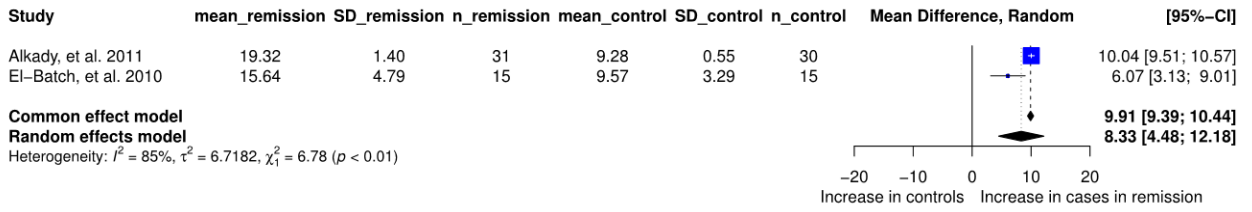
Forest plot of the association between adiponectin and active cases of rheumatoid arthritis without outliers



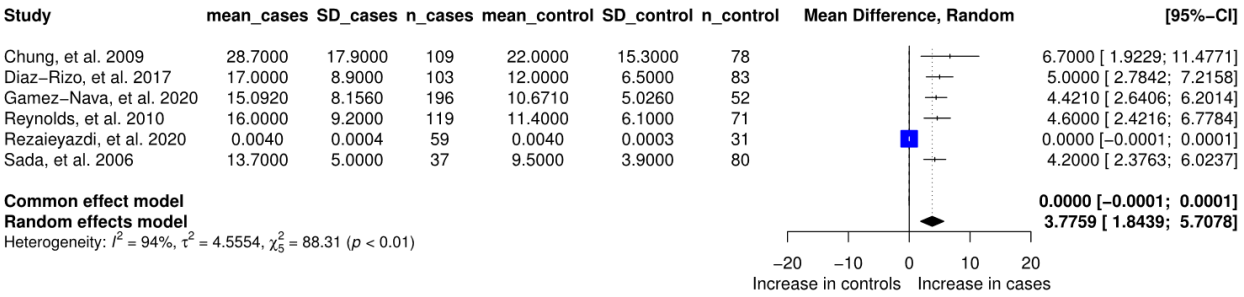
Forest plot of the association between adiponectin and remission cases of rheumatoid arthritis



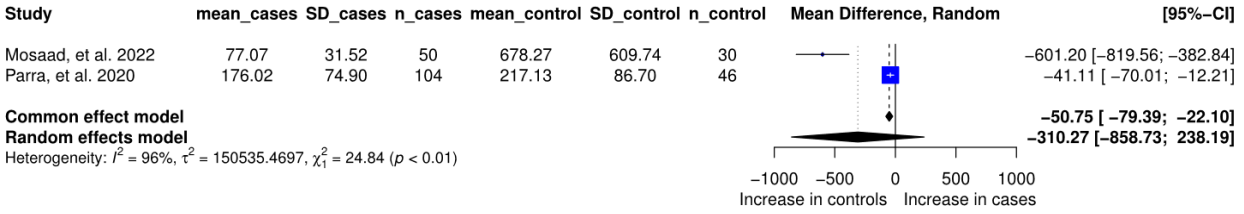
Forest plot of the association between adiponectin and remission cases of rheumatoid arthritis without outliers



Forest plot of the association between adiponectin and systemic lupus erythematosus without outliers



Forest plot of the association between gelsolin and systemic lupus erythematosus



Appendix F: Glossary of technical terms used

RT-PCR – A laboratory technique whereby the reverse transcription of RNA into complementary DNA is combined with the amplification of specific DNA targets utilising PCR.

ELISA – An immunological assay that utilises antibodies, bound to a solid phase, to bind to target antigens which are then bound to enzyme-linked antibodies for detection.

Luminex – A bead-based immunoassay that utilises antibodies, which are bound to microspheres that are internally dyed with fluorophores, to detect antigens using flow cytometry.

Mass spectrometry – A laboratory technique whereby ionised particles are separated by utilising the differences in the ratio of their charges to their respective masses in order to measure their molecular weight.

Random effects model – A statistical model that assumes all of the included studies are a random sample from a universe of possible treatment effects.

Appendix G: Ethics approval letter

School of Public Health
Departement Openbare Gesondheid
Isikolo Sempilo Yoluntu
UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Associate Professor Jill Olivier (Chair)
Departmental Research Committee
University of Cape Town Faculty of Health Sciences
Anzio Road, Observatory 7925, Cape Town, South Africa
T: +27 (0) 21 406 6489
E: jill.olivier@uct.ac.za
W: www.publichealth.uct.ac.za

08 February 2023

STUDENT NUMBER: MRRZEE001

Dear Zeena Morar,

Please be advised that this protocol has been reviewed by the School of Public Health Departmental Research Committee (DRC), agreeing that the study does not require Human Research Ethics Committee (HREC) approval, and has been submitted to Vuyi Mgoqi at the Postgraduate Office, for the Dean's Circular.

Title: Biomarkers for autoimmune disease diagnosis in the public health sector: A systematic analysis

Please upload this to Peoplesoft in the 'Copy of Ethics Approval Letter' section when you do your Intent to Submit.

Kind regards

A/Prof Jill Olivier
Chair: Departmental Research Committee
School of Public Health