

# I too, am America: a review of research on systemic lupus erythematosus in African-Americans

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## ABSTRACT

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disorder that can cause significant morbidity and mortality. A large body of evidence has shown that African-Americans experience the disease more severely than other racial-ethnic groups. Relevant literature for the years 2000 to August 2015 were obtained from systematic searches of PubMed, Scopus, and the EBSCOHost platform that includes MEDLINE, CINAHL, etc. to evaluate research focused on SLE in African-Americans. Thirty-six of the 1502 articles were classified according to their level of evidence. The systematic review of the literature reported a wide range of adverse outcomes in African-American SLE patients and risk factors observed in other mono and multi-ethnic investigations. Studies limited to African-Americans with SLE identified novel methods for more precise ascertainment of risk and observed novel findings that hadn't been previously reported in African-Americans with SLE. Both environmental and genetic studies included in this review have highlighted unique African-American populations in an attempt to isolate risk attributable to African ancestry and observed increased genetic influence on overall disease in this cohort. The review also revealed emerging research in areas of quality of life, race-tailored interventions, and self-management. This review reemphasizes the importance of additional studies to better elucidate the natural history of SLE in African-Americans and optimize therapeutic strategies for those who are identified as being at high risk.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disorder that can cause significant morbidity and mortality. Racial disparities in SLE are undeniable and broadly documented in the scientific literature.<sup>1–16</sup> Sentinel findings, such as those of Fessel,<sup>5</sup> established higher prevalence of the disease in African-American women. Since then, disparities related to psychosocial, social and environmental factors;<sup>1 11 14</sup> disease course and outcomes;<sup>6</sup> barriers to treatment adherence;<sup>9</sup> socio-demographic

variation in incidence, prevalence and treatment outcomes;<sup>4 8 10 12 16</sup> the role of access and quality of care;<sup>3 7</sup> and mortality<sup>2 13 15</sup> have also been documented.

More specifically, a number of multiethnic investigations have shown that African-Americans surpass other racial ethnic groups in terms of renal involvement, including lupus nephritis (LN) and kidney transplantation outcomes;<sup>17–23</sup> damage accrual;<sup>24–27</sup> accrual of American College of Rheumatology (ACR) criteria;<sup>28–32</sup> less prevalent protective allele frequencies<sup>33</sup> and increased risk loci;<sup>34–37</sup> and lower self-reported health-related quality of life (HRQOL).<sup>38–40</sup> The incidence and prevalence of SLE is between 3 and 4 times higher in blacks compared with whites, a major and consistent finding supporting the higher susceptibility of SLE for this racial group.<sup>41 42</sup>

Given the unparalleled SLE burden of this population, it is critical to understand and document within-group disease characteristics. This facilitates targeted consideration for treatment and intervention. Increased understanding may also help to justify and encourage increased minority participation in research, which has been suboptimal<sup>43–46</sup> and impacts the generalisability of clinical trial results, since the low proportion of African-American trial participants is not reflective of the true patient population in the USA.<sup>47</sup>

Considering the importance of improving the evidence base regarding patient-level factors, we performed a literature review of research focused on SLE in African-Americans from January 2000 to August 2015.

## MATERIALS AND METHODS

We searched the databases PubMed, Scopus and the EBSCOHost platform (of 35 databases including MEDLINE, CINAHL, etc) for studies that were focused solely on the prevalence and clinical course of SLE in



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African-Americans or people of the African diaspora published between 2000 and August 2015. The following search terms were used in accordance with each database or platform rules: lupus, systemic lupus erythematosus, African-Americans, blacks, minorities, negro, SLE and/or lupus erythematosus, systemic. The search was completed in September 2015.

The inclusion criteria were peer-reviewed research, prevalence and/or clinical course data, and SLE in African-Americans. All researches that did not contain prevalence data or clinical course data were excluded. In addition, any research article that did not exclusively address the clinical course or prevalence of the people from the African diaspora was also excluded. Literature reviews, case reports and surgical techniques articles were excluded as well as articles not specifically focused on African-Americans. Lastly, authors contributed any known additional articles. A full review was performed on articles identified as being relevant to ensure responsiveness to inclusion and exclusion criteria, and resulting documents were then classified according to an evidence-based medicine criteria proposed by Wright *et al.*<sup>48</sup>

1. high-quality randomised controlled trial
2. lesser quality randomised controlled trial; prospective comparative study
3. case-control study; retrospective comparative study
4. case series
5. expert opinion.

Like-themed articles were grouped together and any articles that did not correspond with others were assigned their own theme designation. The results were then grouped according to the main theme of the articles evaluated, as follows:

- ▶ LN
- ▶ lupus and the environment
- ▶ vitamin D
- ▶ skin disorders
- ▶ traditional chronic disease risk factors
- ▶ genetic studies
- ▶ connections to Africa
- ▶ quality of life
- ▶ race-tailored interventions
- ▶ self-management

## RESULTS AND DISCUSSION

A total of 3721 documents were returned from all electronically searched databases. In total, 1502 articles were identified as pertinent studies for further evaluation based on titles and abstracts. Of these 1502 studies, 74 articles were fully assessed for their relevance to this review, which includes 5 papers the authors contributed. Of the 74 document results, 36 studies met the inclusion criteria of original research articles published in English since 2000 and studies related to the prevalence and clinical course of SLE in African-Americans; 38 articles were literature reviews, case reports and surgical techniques or

articles not specifically focused on African-Americans and thus excluded. The PRISMA flow diagram is included in online supplementary files. A table summarising the objectives, results, conclusions and levels of evidence for each of the 36 included studies is reported.

### Lupus nephritis

We identified two studies that analysed the prevalence and correlates of LN (table 1).<sup>49 50</sup> End-stage renal disease (ESRD) requiring dialysis was the most common complication reported (table 1). Kidney biopsy was the most frequent method applied for diagnosis.<sup>49 50</sup> However, some studies also analysed clinical, serological and immunological data<sup>49</sup> or employed genotyping for prediction of disease risk and outcomes. Risk factors for LN development or progression of diagnosed instabilities identified were hypertension, higher creatinine, proliferative nephritis and decreased glomerular filtration rate (GFR),<sup>49 50</sup> as well as genetic, environmental and socioeconomic factors.<sup>50</sup>

Franco *et al.*<sup>49</sup> investigated predictors of ESRD in a retrospective cohort study of 67 African-American patients with LN with 10 years of follow-up. Biopsies taken between 1996 and 2006 were obtained and clinical, serological and immunological variables were investigated. Independent variables assessed were forms of LN, erythrocyte sedimentation rate (ESR), complement levels, creatinine values, GFR and hypertension. The most common finding was that renal function was more decreased in the proliferative forms of LN, whereas the less common findings were that patients with class V LN had significantly less risk to progress to ESRD (p values<0.05), and on subgroup analysis, neither low C3 nor low C4 levels were associated with ESRD. Finally, the authors concluded that hypertension, higher creatinine, proliferative nephritis and decreased GFR are associated with ESRD requiring dialysis.

In an expert opinion piece, Lea discussed LN as more common and severe in African-American women and higher incidence of progression to ESRD in African-Americans, despite aggressive immunosuppressive therapies employed in LN.<sup>50</sup> She posits that racial disparities seem to be due to genetic, environmental and socioeconomic factors. Lea recognises that hypertension and proteinuria are well-defined prognostic factors that significantly impact the course of renal disease progression for most forms of renal disease, but points out that clinical trials in LN to date have not evaluated the role of aggressive antihypertensive or antiproteinuric therapies in retarding renal disease progression. Thus, she concludes that additional studies are needed to better elucidate the natural history of LN in African-Americans and to optimise therapeutic strategies for those who are identified as being at high risk.

### Lupus and the environment

We identified three studies analysing environmental impacts on SLE in African-Americans (table 2). Carroll

**Table 1** Summary of two studies examining lupus nephritis (LN) in African-Americans

Author, year	N	Objective	Results	Conclusions	Level of evidence
Franco <i>et al</i> , 2010 <sup>49</sup>	67	To correlate clinical, serological and immunological variables with the development of ESRD requiring dialysis in the African-American population	Renal function was more decreased in the proliferative forms of LN. Erythrocyte sedimentation rate was increased mostly in classes III, IV and V. Complement levels were uniformly decreased in the population studied. C4 was more significantly decreased in the proliferative forms of LN. Higher creatinine values, low GFR, class IV LN and hypertension were associated with ESRD in this population. Patients with class V LN had significantly less risk to progress to ESRD (p values<0.05).	Hypertension, higher creatinine, proliferative nephritis and decreased GFR are associated with ESRD requiring dialysis.	III
Lea, 2002 <sup>50</sup>	N/A	To explore the higher incidence of progression to ESRD in African-Americans	Hypertension and proteinuria are well-defined prognostic factors that significantly impact the course of renal disease progression for most forms of renal disease. Clinical trials in LN to date have not examined the role of aggressive antihypertensive or antiproteinuric therapies in retarding renal disease progression.	Additional studies are needed to better elucidate the natural history of LN in African-Americans and to optimise therapeutic strategies for those who are identified as being at high risk.	V

ESRD, end-stage renal disease; GFR, glomerular filtration rate; N/A, not available.

*et al*<sup>51</sup> assessed links between environmental exposures and autoimmunity (measured as presence of antinuclear antibodies (ANAs)) among a population of Gullah African-Americans in South Carolina. The study population included 10 patients with SLE, 61 of their

first-degree relatives and 9 unrelated controls. Detailed lifetime exposure assessments were performed over a 3-year period and captured a detailed residential and occupational history, questions about diet (including local seafood consumption), ascertainment of lifestyle

**Table 2** Summary of three articles relating lupus and the environment in African-Americans

Author, year	N	Objective	Results	Conclusions	Level of evidence
Carroll <i>et al</i> , 2014 <sup>51</sup>	80	To assess links between environmental exposures and autoimmunity	With more meticulously collected exposure data, chemicals associated with ANA status were identified	Even with a small sample significant exposure–outcome relationships can be detected	III
Terrell <i>et al</i> , 2008 <sup>52</sup>	N/A	To use CBPR practices to educate impacted residents and enable their participation in efforts to get a nearby waste site remediated	The impacted community was involved in information gathering and analysis and gained necessary skills to assess current conditions and prevent duplication of injustices	CBPR methods were used to empower a community and enable a community-driven remediation plan to be endorsed by the governing agency	IV
Williams <i>et al</i> , 2009 <sup>53</sup>	13	To explore patients' experiences and concerns with their living environment and their perceptions of environmental effects on their health and disease status	Participants had the perception that there are components in the environment that people come into contact with that are potentially hazardous, and there was a shared concern about the presence of toxic waste in the soil in their community	The community recognises need for education, environmental change and the impact of public policy on these efforts	III

ANA, antinuclear antibodies; CBPR, community-based participatory research; N/A, not available.

factors (including well water use, smoking status, pesticide use) and health questions (including medication history). The groundwater and soil chemical survey data were measured in 2005 and made available by the United States Geological Survey, and the strip data used for validation consisted of metal concentrations measured in soil samples taken from a relatively dense network of sites that were originally sampled in 2011. Authors followed dimension reduction and selection methods, and fit logistic spatial Bayesian models to explore the relationship between the outcome of interest (presence of ANA) and environmental exposures, adjusting for personal variables. Their analysis also included a validation 'strip' where they interpolated information from a specific geographic area for a subset of the study population that lives in that vicinity. With more meticulously collected exposure data, they were able to find heavy metals, pesticides and organochlorines in the groundwater and/or soil (including lead, chromium, copper, manganese and arsenic) associated with ANA status. Authors concluded that such efforts could ultimately lead to novel prediction tools to identify individuals most likely to develop SLE-related autoimmunity and could inform efforts to prevent progression to autoimmune disease.

Terrell *et al*<sup>52</sup> conducted community-based participatory research (CBPR) as part of a collaborative partnership between the University at Buffalo and the Toxic Waste Lupus Coalition to investigate the high prevalence of lupus in a defined geographic area and whether cases of disease were linked to chemicals found at a nearby New York State Superfund site in East Buffalo. Contaminants of concern that were common to the prior Carroll study included lead and arsenic. The target research population consisted of African-American men and women who lived in the 34th and 35th census tracts located on the east side of Buffalo, New York, and the project was 5 years in duration. During the course of the project, CBPR practices were used to educate impacted residents and enable their participation in efforts to get a nearby contaminated waste site remediated. Community members were active participants in the development of the plan to clean-up the toxic site. The authors were able to show that through CBPR methods a strategy could be developed and implemented at the community level that resulted in actions that have either directly or indirectly improved the quality of life for participants and other affected community residents.

In a related qualitative examination, Williams *et al*<sup>53</sup> explored patients' experiences and concerns with their living environment and their perceptions of environmental effects on their health and disease status in the same urban Buffalo, New York, African-American community with a high burden of lupus and other autoimmune diseases. Thirteen African-American community members, who were diagnosed with lupus, participated in two focus group discussions. A theory-

driven immersion crystallisation approach was used for data analysis, and five themes emerged. These included environmental impact on illness, exposure to environmental hazards, community awareness about lupus, environmental determinants of lupus and strategies for environmental action. Results from participants' experiences showed a need for improvement in environmental conditions as well as different strategies to raise awareness of lupus and other autoimmune diseases in at-risk urban minority communities.

### Vitamin D

Disparities in vitamin D status are similar to those seen in SLE, in that the prevalence and severity of vitamin D deficiency are highest among African-Americans compared with other racial groups in the USA. The high prevalence of vitamin D deficiency among African-Americans has been attributed to higher melanin content in the skin, therefore blocking the conversion of UVB from sunlight to vitamin D. The problem is exacerbated in patients with SLE who often have photosensitivity and are advised to avoid direct sun exposure.<sup>54</sup> This cultural environmental risk factor is highlighted by the fact that Sierra Leone Africans have significantly higher serum 25-hydroxyvitamin D levels than their Gullah African-American relatives.<sup>55</sup>

A study by Hoffecker *et al*<sup>56</sup> evaluated serum 25-hydroxyvitamin D levels among 59 African-American Gullah women with SLE and 59 unaffected controls from the Sea Island region of South Carolina and examined relationships between antitelomere antibodies, telomere length (a measure of cellular ageing) and vitamin D status (table 3).

ELISA was used to measure antitelomere antibody levels, and telomere length was measured in genomic DNA of peripheral blood mononuclear cells (PBMCs) by monochrome multiplex quantitative PCR. A non-chromatographic radioimmunoassay was used to measure serum 25-hydroxyvitamin D levels. The results showed that patients with SLE had significantly shorter telomeres and higher antitelomere antibody titres compared with age-matched and gender-matched unaffected controls. There was also a positive correlation between antitelomere antibody levels and disease activity among patients, as well as a significant correlation of shorter telomeres with lower 25-hydroxyvitamin D levels in both patients and controls. The authors' findings suggest that antitelomere antibody levels may be used as a biomarker of status of SLE and disease activity. A subset of the patients with SLE were chosen for secondary examination, and the authors found that the patients who remained vitamin D deficient tended to have shorter telomeres than those patients whose 25-hydroxyvitamin D levels came back to normal levels. This suggests that increasing 25-hydroxyvitamin D levels in African-American patients with SLE may be beneficial in increasing and maintaining telomere length and thereby preventing cellular ageing.



**Table 3** Summary of an article exploring vitamin D in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Hoffecker <i>et al</i> , 2013 <sup>56</sup>	118	To evaluate relationships between vitamin D status, cellular ageing (telomere length) and antitelomere antibodies among African-American Gullah women with SLE.	Patients with SLE had higher antitelomere antibody titres and significantly shorter telomeres compared to age-matched and gender-matched controls without SLE. The patients who remained vitamin D deficient tended to have shorter telomeres than those patients whose 25-hydroxyvitamin D levels came back to normal levels.	Increasing 25-hydroxyvitamin D levels in African-American patients with SLE may be beneficial in maintaining telomere length and preventing cellular ageing. Antitelomere antibody levels may be a promising biomarker of SLE status and disease activity.	III

SLE, systemic lupus erythematosus.

### Skin disorders

Only one identified study conducted a historical review of 60 scalp biopsies from African-American patients to elucidate important clues regarding the diagnosis of scarring alopecia from hot petroleum-based hair treatments and tight hair braiding that are more prevalent in or exclusive to African-Americans (table 4).<sup>57</sup>

Serial vertical and horizontal sections from 25 cases of central centrifugal cicatricial alopecia (CCCA), 5 cases of frontal fibrosing alopecia, 22 cases of traction alopecia (TA), 2 cases of alopecia areata, 3 cases of discoid lupus erythematosus and 3 cases of hair breakage were examined. Miteva *et al* observed that there are a few characteristic features of the African-American scalp, which include asymmetrical outer root sheath, the elliptical shape of the hair shaft, golf club-shaped bulb and paired grouping of hair follicles. A few indications for a diagnosis of TA were preserved sebaceous glands along with follicular miniaturisation and dropout. Characteristics that suggest a CCCA diagnosis include goggles, naked hair shafts in fibrous streamers and premature desquamation of the inner root sheath. The authors point out that the clues they report

may help dermatopathologists to recognise a scalp biopsy from an African-American patient, make the most probable diagnosis by connecting the clues and understand the morphological basis for the susceptibility of the African hair to damage and distinguish this from lupus-related alopecia.

### Traditional chronic disease risk factors

Four identified studies evaluated traditional chronic disease risk factors, particularly cardiovascular disease (CVD) risk factors, in African-Americans with SLE, including a total of 64 725 African-American women (136 cases and 64 589 controls) (table 5).

Formica *et al*<sup>58</sup> performed a prospective investigation of the associations of smoking and alcohol consumption with incident SLE in the 64 500 African-American women over 4 years. They evaluated demographic characteristics, reproductive and medical histories, smoking and alcohol consumption. Incident cases of SLE were established by follow-up questionnaires. A new diagnosis of SLE was found in 67 women, as well as use of appropriate medication for their illness. Authors

**Table 4** Summary of an article exploring skin disorders in African-Americans

Author, year	N	Objective	Results	Conclusions	Level of evidence
Miteva <i>et al</i> , 2012 <sup>57</sup>	60	To perform a retrospective review of 60 scalp biopsies from African-American patients	Features characteristic of the African-American scalp include: golf club-shaped bulb, elliptical shape of the hair shaft, asymmetrical outer root sheath and paired grouping of hair follicles	The clues reported here aim to help the dermatopathologists to recognise at a glance that they are dealing with a scalp biopsy from an African-American patient; make the most probable diagnosis by connecting the clues; and understand the morphological basis for the susceptibility of the African hair to damage	IV

**Table 5** Four studies of traditional chronic disease risk factors in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Formica <i>et al</i> , 2003 <sup>58</sup>	64 500	To prospectively investigated associations of smoking and alcohol consumption with incident SLE in the Black Women's Health Study	67 women reported a new diagnosis of SLE and use of appropriate medication for that illness. In multivariate analyses, an increased risk of SLE among smokers was observed, but no effect of alcohol consumption on risk.	The inverse association of alcohol consumption with SLE found in studies of prevalent disease may have resulted from women with SLE giving up drinking	II
Williams <i>et al</i> , 2009 <sup>59</sup>	124	To investigate the relationship between carotid atherosclerosis and inflammation in African-American women	Tumour necrosis factor- $\alpha$ was significantly related to lupus, hypertension, body mass index and carotid intima media thickness, indicating this could be an important factor to consider in future studies of cardiovascular risk in African-American women with lupus.	There may be other factors in the link between SLE and CVD	III
Williams <i>et al</i> , 2008 <sup>60</sup>	101	To characterise the prevalence of traditional CVD risk factors and the markers of subclinical atherosclerosis	There were significant differences between SLE cases and controls in the areas of current smoking (18% of SLE cases, 15% of controls, $p=0.01$ ), average fasting glucose (85 mg/dL in SLE cases, 98 mg/dL in controls, $p=0.02$ ) and high blood pressure (68% of SLE cases, 42% of controls, $p=0.02$ ). SLE cases also showed non-significantly higher high-density lipoprotein cholesterol levels, lower low-density lipoprotein cholesterol levels and lower body mass index.	Larger studies are recommended to elucidate non-traditional mechanisms that may modulate some of the increased risk for CVD associated with SLE in women	III
Liang <i>et al</i> , 2002 <sup>62</sup>		Determining the biology, risk factors and the prevention of atherosclerosis in individuals with SLE	Not a great deal is known about the risk factors for SLE in African-Americans, although there are data to suggest that they may not be identical to those seen in Caucasian populations.	The study of the best and most effective means to prevent atherosclerotic vascular disease in SLE and in African-Americans with SLE should be a major priority	V

CVD, cardiovascular disease; SLE, systemic lupus erythematosus.

observed an increased risk of SLE among smokers, but no effect of alcohol consumption on risk, suggesting that the inverse association of alcohol consumption with SLE found in studies of prevalent disease may have resulted from women with SLE giving up drinking.

Williams *et al*<sup>59</sup> performed a case-control study of 41 lupus cases and 83 controls to evaluate the relationship between carotid atherosclerosis and inflammation in African-American women, according to disease status. Data collected included an ultrasound of the carotid arteries, a physical examination, fasting blood draw and a questionnaire. Assessment of traditional CVD risk factors included age, household income, education level, smoking habits (current and past use), hypertension, family history of CVD (myocardial infarction (MI), stroke or sudden death in a first-degree relative before the age of 60 years), diabetes (previous diagnosis and/or current use of oral hypoglycaemic agents or insulin) and fasting glucose levels, physical activity, body mass index (BMI) and total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglyceride levels. Authors observed differences between cases and controls with carotid intima media thickness (IMT) and traditional cardiovascular risk factors, although few of these differences reached statistical significance. However, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) was significantly related to carotid IMT, lupus, BMI and hypertension, so authors concluded that TNF- $\alpha$  may be an important factor to assess and consider in future studies of cardiovascular risk in African-American women with lupus.

In a related case-control study of 28 lupus cases and 73 controls, Williams *et al*<sup>60</sup> evaluated the prevalence of traditional CVD risk factors and the markers of subclinical atherosclerosis between African-American SLE cases and controls. The authors found significant differences between SLE cases and controls in high blood pressure (68% of SLE cases, 42% of controls,  $p=0.02$ ), average fasting glucose (85 mg/dL in SLE cases, 98 mg/dL in controls,  $p=0.02$ ) and current smoking (18% of SLE cases, 15% of controls,  $p=0.01$ ). SLE cases also found higher levels of HDL-c, lower LDL-c and lower BMI compared with controls, although these differences were not statistically significant. Authors concluded that since the study sample was small and highly select, larger studies are recommended to elucidate non-traditional mechanisms that may modulate some of the increased risk for CVD associated with SLE in women. In a cross-sectional study of 51 predominantly African-American women with lupus, Ravenell *et al* observed that accelerated age-matched and sex-matched carotid atherosclerotic plaque formation occurred in lupus. Using traditional multivariable modelling, extent of atherosclerotic plaque was associated with lack of ACE inhibitor use, and low vitamin D and high cholesterol levels. In machine learning modelling, lack of hydroxychloroquine use, traditional risk factors and number of years

with lupus were also important factors that increased prediction of disease.<sup>61</sup>

In an expert opinion piece, Liang *et al*<sup>62</sup> discussed atherosclerotic vascular disease (ASVD) (including MI, angina, peripheral vascular disease and stroke) in African-Americans with SLE. Liang noted that ASVD is accelerated and occurs earlier in age, suggesting that ASVD in people with SLE may be a different disease. Given that the best study of risk factors shows that even accounting for the known factors (ie, smoking, obesity, sedentary lifestyle, high LDL-c) SLE and/or its treatment (glucocorticoids) is by far the most important, Liang posits that our current management of cardiovascular risk factors in SLE patients with ASVD and our adherence to national guidelines for prevention is substandard. Since very little is known about the risk factors in African-Americans with SLE, Liang concluded by suggesting that the study of the best and most effective means to prevent ASVD in SLE and in African-Americans with SLE should be a major priority.

### Genetic studies

We identified nine studies that investigated genetic correlates in a total of 5935 African-American patients with SLE (table 6).<sup>63–71</sup> Apolipoprotein L1 (APOL1) gene risk alleles were the most common risk loci investigated (table 6). Genotyping was the most frequent mode of diagnosis,<sup>63 64 67 68</sup> specifically with the use of DNA sequencing or ELISA methods.<sup>65</sup>

Freedman *et al*<sup>64</sup> evaluated whether the APOL1 nephropathy risk alleles G1/G2, common in African-Americans and rare in European Americans, contributed to the ethnic disparity in risk for LN and ESRD in 855 African-American SLE patients with LN-ESRD (cases) and 534 African-American SLE patients without nephropathy (controls). The authors genotyped two nephropathy alleles, APOL1 G1 and G2, and used logistic regression to test for association under a recessive genetic model. Independent variables assessed were sex, age at SLE diagnosis, time from SLE diagnosis to development of LN-ESRD and ancestry admixture. Twenty-five per cent of LN-ESRD cases and 12% of SLE non-nephritis controls had two nephropathy alleles, concluding that the G1/G2 risk alleles were strongly associated with SLE-ESRD. The authors concluded that APOL1 G1/G2 alleles strongly impact the risk of LN-ESRD in African-Americans, as well as the time to progression to ESRD, and the high frequency of these alleles in African-Americans with near absence in European Americans appears to explain an important proportion of the increased risk of LN-ESRD in African-Americans.

Larsen *et al*<sup>63</sup> re-examined 546 renal biopsies from African-American patients with SLE to investigate the association of APOL1 risk alleles with SLE-associated collapsing glomerulopathy. After genotyping APOL1 risk alleles using DNA from archived biopsy tissue, 26 cases of collapsing glomerulopathy were identified. In a recessive model, two APOL1 risk alleles resulting in 5.4-fold

**Table 6** Nine genetic studies in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Larsen <i>et al</i> , 2013 <sup>63</sup>	546	To investigate whether APOL1 risk alleles associate with SLE-associated CG	Evaluation of biopsies from 188 cases with zero risk alleles, 264 cases with one risk allele and 94 cases with two risk alleles revealed 26 cases with CG, and APOL1 was strongly associated with SLE-associated CG ( $p < 0.001$ ).	APOL1 genotyping of African-American patients with SLE might help identify patients at risk for CG, a phenomenon with a poor prognosis often resistant to treatment	III
Freedman <i>et al</i> , 2014 <sup>64</sup>	1389	To investigate whether the APOL1 nephropathy risk alleles G1/G2, common in African-Americans and rare in European Americans, contribute to the ethnic disparity in risk	Two risk alleles, G1/G2, were strongly associated with SLE-ESRD, with 25% of cases and 12% of controls having two nephropathy alleles (OR 2.57, recessive model $p = 1.49 \times 10^{-9}$ ). The population-attributable risk (adjusted for age, sex and admixture) for ESRD among patients with G1/G2 polymorphisms was 0.26 compared with 0.003 among European American patients. The mean time from SLE diagnosis to ESRD development was about 2 years earlier among individuals with APOL1 risk genotypes ( $p = 0.01$ ).	The high frequency of APOL1 G1/G2 alleles in African-Americans with near absence in European Americans explains an important proportion of the increased risk of LN-ESRD in African-Americans	III
Namjou <i>et al</i> , 2012 <sup>65</sup>	5	To assess and characterise C1q deficiency in an African-American lupus pedigree	A novel homozygote start codon mutation in C1qA gene that changes amino acid methionine to arginine at position 1 (Met1Arg) was identified in an African-American patient with lupus and C1q deficiency and her family members, along with absence of total complement activity consistent with a recessive pattern of inheritance.	The identification of new mutation in C1qA gene that disrupts the start codon (ATG to AGG (Met1Arg)) expands the knowledge and importance of the C1q gene in the pathogenesis of lupus in the high-risk African-American population	III
Ramos <i>et al</i> , 2013 <sup>66</sup>	3364	To analyse variation in reactive intermediate genes for association with SLE in two populations with African ancestry	The glutathione reductase gene GSR (rs2253409; $p = 0.0014$ , OR 1.26, 95% CI 1.09 to 1.44) was the most significant single SNP association in African-Americans. In the Gullah, the NADH dehydrogenase NDUFS4 (rs381575; $p = 0.0065$ , OR 2.10, 95% CI 1.23 to 3.59) and NO synthase gene NOS1 (rs561712; $p = 0.0072$ , OR 0.62, 95% CI 0.44 to 0.88) were most strongly associated with SLE. When both populations were analysed together, GSR remained the most significant effect (rs2253409; $p = 0.00072$ , OR 1.26, 95% CI 1.10 to 1.44).	Results suggest distinct patterns of association with SLE in African-derived populations	III

Continued



**Table 6** Continued

Author, year	N	Objective	Results	Conclusions	Level of evidence
Ruiz-Narvaez <i>et al</i> , 2011 <sup>67</sup>	1148	To conduct a screening of the MHC region for SNPs and the deletion of the <i>C4A</i> gene in a SLE case-control study	The rs9271366 SNP was most strongly associated with SLE (OR, OR=1.70, $p=5.6 \times 10^{-5}$ ). Conditional haplotype analysis revealed three other SNPs, rs204890 (OR=1.86, $p=1.2 \times 10^{-4}$ ), rs2071349 (OR=1.53, $p=1.0 \times 10^{-3}$ ), and rs2844580 (OR=1.43, $p=1.3 \times 10^{-3}$ ) to be associated with SLE independent of the rs9271366 SNP. A genotype score combining the four newly identified SNPs showed an additive risk according to the number of high-risk alleles (OR=1.67 per high-risk allele, $p<0.0001$ ).	There are four independent signals in the MHC region associated with risk of SLE in African-American women	III
Sánchez <i>et al</i> , 2011 <sup>68</sup>	3748	To examine whether some of the same susceptibility loci increase lupus risk in African-American individuals	Authors found the first evidence of genetic association between lupus in African-American patients and five susceptibility loci ( <i>C8orf13-BLK</i> , <i>BANK1</i> , <i>TNFSF4</i> , <i>KIAA1542</i> and <i>CTLA4</i> ; $p=8.0 \times 10^{-6}$ , $p=1.9 \times 10^{-5}$ , $p=5.7 \times 10^{-5}$ , $p=0.00099$ , and $p=0.0045$ , respectively). Authors also confirmed the genetic association between lupus and five additional lupus susceptibility loci ( <i>ITGAM</i> , <i>MSH5</i> , <i>CFB</i> , <i>STAT4</i> and <i>FCGR2A</i> ; $p=7.5 \times 10^{-11}$ , $p=5.2 \times 10^{-8}$ , $p=8.7 \times 10^{-7}$ , $p=0.0058$ , and $p=0.0070$ , respectively), and provided evidence of genome-wide significance for the association between lupus in African-American patients and <i>ITGAM</i> and <i>MSH5</i> (HLA region).	Novel genetic susceptibility loci for lupus were identified in African-Americans and authors demonstrated that the majority of lupus susceptibility loci examined confer lupus risk across multiple ethnicities	III
Dozmorov <i>et al</i> , 2013 <sup>70</sup>	40	To study the higher rates of lupus-related ESRD in African-Americans	A strong link was detected between APOL1 G1 and G2 variants and LN-ESRD in African-Americans.	Findings further support the role of G1 and G2 variants of APOL1 gene in higher rates of lupus-related ESRD in African-Americans	III
Wu <i>et al</i> , 2003 <sup>72</sup>	361	To explore the -844C genotype in African-Americans with SLE	There was enrichment of the -844C homozygous genotype in the patients with SLE compared with ethnically matched controls.	Findings further support the potential importance of SNPs in regulatory regions	III
Freedman <i>et al</i> , 2013 <sup>69</sup>	N/A	To review the current status of APOL1-associated nephropathy	There is a genetic association between the APOL1 gene and several severe non-diabetic forms of kidney disease in African-Americans that nears Mendelian inheritance patterns. This associated accounts for and account for a large percentage of glomerulosclerosis in populations of African ancestry.	Emerging data support an important role for APOL1 in the progression of kidney disease	V

APOL1, apolipoprotein L1; CG, collapsing glomerulopathy; ESRD, end-stage renal disease; HLA, human leukocyte antigen; LN, lupus nephritis; MHC, major histocompatibility complex; N/A, not available; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.

(95% CI 2.4 to 12.1) higher odds of developing SLE-associated collapsing glomerulopathy ( $p < 0.001$ ), and authors concluded that APOL1 was strongly associated with SLE-associated collapsing glomerulopathy ( $p < 0.001$ ). Their findings suggest that APOL1 genotyping of African-American patients with SLE might help identify patients at risk for collapsing glomerulopathy, an entity with a poor prognosis that is often resistant to treatment.

Ramos *et al*<sup>66</sup> analysed variation in reactive intermediate genes and their association with SLE in two populations of African ancestry by analysing a total of 244 single-nucleotide polymorphisms (SNPs) from 53 regions in non-Gullah African-Americans (1432 cases and 1687 controls) and the genetically more homogeneous Gullah of the Sea Islands of South Carolina (133 cases and 112 controls). In the Gullah population, the NO synthase gene NOS1 (rs561712) and the NADH dehydrogenase NDUF54 (rs381575) were most strongly associated with SLE. When both populations of African-Americans were analysed together, the glutathione reductase gene GSR remained the most significant single SNP association (rs2253409). Haplotype and two-locus interaction analyses uncovered different loci in each population. Authors concluded that their findings suggest distinct patterns of association with SLE in African-derived populations and that specific loci may be more strongly associated within select population groups.

Ruiz-Navarez *et al*<sup>67</sup> conducted a nested case-control study to comprehensively analyse the major histocompatibility complex (MHC) region in relationship to SLE in African-Americans. Authors conducted a screening of the MHC region for 1536 potential SNPs and the deletion of the *C4A* gene in participants in the prospective Black Women's Health Study, which included 380 SLE cases and 765 age-matched controls. Authors also performed genotyping on 1509 ancestral informative markers to estimate European ancestry in order to control for population stratification due to population admixture. Authors found four independent SNPs in the MHC region associated with risk of SLE in African-American women. The most strongly associated SNP with SLE was rs9271366 near the *HLA-DRB1* gene. Conditional haplotype analysis revealed three other SNPs (rs204890, rs2071349 and rs2844580) that were associated with SLE independent of the rs9271366 SNP. A genotype score combining the four newly identified SNPs showed an additive risk according to the number of high-risk alleles.

Sanchez *et al*<sup>68</sup> undertook a study to examine whether some of the susceptibility loci identified in patients with lupus of Asian or European ancestry increase lupus risk in 1724 patients with lupus and 2024 healthy controls of African-American descent. SNPs tagging the following 15 independent lupus susceptibility loci were genotyped: *PTPN22*, *FCGR2A*, *TNFSF4*, *STAT4*, *CTLA4*, *PDCD1*, *PXK*, *BANK1*, *MSH5* (human leukocyte antigen (HLA) region), *CFB* (HLA region), *C8orf13-BLK* region, *MBL2*,

*KIAA1542*, *ITGAM* and *MECP2/IRAK1*. Authors found evidence of genetic association between lupus in African-American patients and five susceptibility loci (*C8orf13-BLK*, *BANK1*, *TNFSF4*, *KIAA1542* and *CTLA4*), the first of its kind. Furthermore, they confirmed the genetic association between lupus and five additional lupus susceptibility loci (*ITGAM*, *MSH5*, *CFB*, *STAT4* and *FCGR2A*) and provided evidence, for the first time, of genome-wide significance for the association between lupus in African-American patients and the two loci of *ITGAM* and *MSH5* (HLA region). Authors concluded that their findings provide evidence of novel genetic susceptibility loci for lupus in African-Americans.

Namjou *et al*<sup>65</sup> evaluated the C1q genomic region in an African-American lupus pedigree that included two SLE cases and three blood relatives and spouse. The C1q A, B and C gene cluster was obtained from the genomic DNA of the patient and sequenced by next-generation sequencing in order to assess and characterise C1q deficiency in the African-American lupus pedigree. The identified mutation was further confirmed by direct Sanger sequencing method in the patient and all blood relatives. C1q levels in serum were measured using the sandwich ELISA method. In an African-American patient with lupus and C1q deficiency, the authors identified and confirmed a novel homozygote start codon mutation in the C1qA gene that changes the amino acid methionine to arginine at position 1. This Met1Arg mutation prevents protein translation (Met1Arg). Mutation analyses of the patient's family members also revealed that the patient's deceased brother, who also had lupus, had the Met1Arg homozygote mutation with absence of total complement activity consistent with a recessive pattern of inheritance. Authors concluded that the identification of new mutation in C1qA gene that disrupts the start codon (ATG to AGG (Met1Arg)) has not been reported previously, and it therefore expands the knowledge and importance of the C1q gene in the pathogenesis of lupus, especially in the high-risk African-American population.

Since the Fas ligand (*FasL*) gene is located on human chromosome 1q23, a region that shows linkage to the SLE phenotype, Wu and associates (2003) sought to explore the importance of the SNP identified at nucleotide position -844 in the 5' promoter of the *FasL* gene in African-American patients with SLE. The -844C genotype has been associated with increased basal activity and higher levels of peripheral blood fibrocytes, and there are concerns that the -844C homozygous genotype may lead to the increased expression of FasL, to altered FasL-mediated signalling in lymphocytes, and to enhanced risk for autoimmunity. Analysis of 211 African-American patients with SLE, compared with 150 ethnically matched normal controls, revealed enrichment of the -844C homozygous genotype in the patients with SLE ( $p = 0.024$ ). Authors concluded that findings further support the potential importance of SNPs in regulatory regions and suggest that differences in the

regulation of FasL expression may contribute to the development of the autoimmune phenotype.<sup>72</sup>

In an effort to examine differences in complex regulatory processes between healthy controls and autoimmune patients, Dozmorov *et al*<sup>70</sup> compared changes in regulatory gene interconnections in Epstein-Barr virus transformed hyper-responsive B cells from patients with SLE and normal control B cells. Authors screened cell lines from 20 African-American female patients with lupus and 20 African-American female controls to identify cell lines that responded to receptor stimulation and exhibited a hyper-responsive B cell phenotype associated with B cells of patients with SLE. Traditional analysis of differential gene expression was performed, as well as the dynamic of gene expression variation, in order to establish model networks of functional gene expression. Known transcription factors emerged from this Pathway Dysregulation Analysis, and authors found that transcriptional regulators did in fact uniquely activate stimulated B cells from patients with SLE. In an expert opinion piece, Freedman<sup>69</sup> discussed the genetic association between the APOL1 gene and several severe non-diabetic forms of kidney disease in African-Americans. The authors suggest that these associations approach Mendelian inheritance patterns and might account for a large proportion of glomerulosclerosis in populations of African ancestry. They also suggest that APOL1 has an important role in the progression of diverse aetiologies of kidney disease, in concert with requisite environmental (genexenvironment) and inherited (genexgene) interactions.

### Connections to Africa

We identified four studies explicitly examining African ancestry as it relates to SLE in African-Americans (table 7). Given the documented association between the heterozygous C4A gene deletion and SLE in US Caucasians and African-Americans, Fraser *et al* performed C4A gene analysis in DNA samples from 18 African-Americans and Afro-Caribbeans to define the haplotypes with C4A-deleted alleles in African-Americans.<sup>73</sup> There were 14 unrelated subjects and 2 sisters also included from 17 of 50 African-American or Afro-Caribbean families who were previously studied for HLA-complement haplotypes and 2 unrelated HLA-B53-positive subjects for whom complotypes were not available. The group of subjects studied was composed of three healthy controls, three healthy first-degree relatives of probands with rheumatoid arthritis or lupus, four subjects with rheumatoid arthritis and one subject each with overlap syndrome, undifferentiated connective tissue disease and fibromyalgia. Haplotypes investigated were based on limited data from populations of sub-Saharan African (SSAF) ancestry with SLE and normal SSAFs, suggesting that haplotypes bearing HLA-B44, B53 and DRB1p1503 are the major sources of excess C4A-deleted alleles in African-Americans with SLE. The methods used in this analysis included serological HLA-A, B and DR typing, HLA-B and DRB1 molecular typing, complotyping and Southern C4A gene analysis. DNA

samples with C4A gene deletions were included as positive controls. Authors defined at least one haplotype bearing a C4A null allele and/or C4A gene deletion in 16 subjects. Haplotypes HLA-DRB1p1503, HLA-B53, B44031 or B18 and HLA-DRB1p0301, and HLA-B53 and B8 were observed in conjunction with C4A gene deletions. This is the first study to define the HLA haplotypes bearing C4A gene deletions in populations of SSAF ancestry, and authors conclude that their findings lend support to the concept that the pool of haplotypes with C4A gene deletions of SSAF origin may exert an effect on the MHC-modulated risk of SLE in African-Americans that may be equivalent to the effect of haplotypes derived from genetic admixture with Caucasian genes.

To define whether a lupus prevalence gradient exists (ie, high disease load of SLE in African-Americans and perception that lupus is relatively rare in Africa), Gilkeson *et al* began a study of autoimmunity prevalence in two unique but ancestrally related cohorts: 70 young African women served by the West Africa Fistula Foundation in Bo, Sierra Leone, and 107 age-matched African-American Gullah female controls with no known relatives with lupus and no symptoms of lupus from the Sea Islands of South Carolina. The Gullah are unique in their low genetic admixture and their direct ancestral link to Sierra Leoneans.<sup>55</sup> Authors assessed the prevalence of lupus serum autoantibodies, serological evidence of specific infections and levels of serum 25-OH vitamin D in both cohorts. Their results found there was a significantly increased prevalence of antiphospholipid and anti-Sm antibodies in the Sierra Leone cohort, but there was a similar prevalence of serum ANAs in the two cohorts. The women from Sierra Leone had significantly higher seropositivity to common viral infections, while the women in the Gullah population had lower serum 25-OH vitamin D levels. Authors concluded that while their data suggest that the prevalence of autoimmunity is similar in the two populations, there are significant environmental differences that may impact progression to autoimmune disease.

In a related study, Kamen *et al*<sup>74</sup> used data from an ongoing cohort study of lupus in the Gullah population to define the genetic and environmental factors contributing to SLE in this population. Authors summarised disease characteristics and serological profiles for 184 patients with SLE, 144 unaffected first-degree relatives and 144 matched unrelated, unaffected control subjects. They observed a high prevalence of SLE multiplex families, malar rash, discoid rash, photosensitivity and oral/nasal ulcerations, but a lower prevalence of haematological and pleuropericardial disease than has been reported in other African-American cohorts. This population had similar overall renal and central nervous system involvement, number of ACR disease criteria met and Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI) scores to other cohorts. Lupus-specific antibodies were more prevalent in the women than in the men in this cohort, although male

**Table 7** Summary of four articles on connections to Africa in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Fraser <i>et al</i> , 2000 <sup>73</sup>	18	To define the haplotypes with C4A-deleted alleles in African-Americans	Haplotypes HLA-DRB1p1503, HLA-B53, B44031 or B18 and HLA-DRB1p0301 and HLA-B53 and B8 were observed in conjunction with C4A gene deletions.	This is the first study to define the HLA haplotypes bearing C4A gene deletions in populations of sub-Saharan African ancestry	III
Gilkeson <i>et al</i> , 2011 <sup>55</sup>	184	To define whether a lupus gradient exists between African-Americans and Africans	The prevalence of serum antinuclear antibodies in the two cohorts was comparable, though there was a significantly increased prevalence of antiphospholipid and anti-Sm antibodies in the Sierra Leone cohort. Seropositivity for common viral infections was significantly higher in women from Sierra Leone, while serum 25-OH vitamin D levels were drastically lower in the Gullah population.	While the prevalence of autoimmunity is similar in the two populations, there are significant environmental differences that may impact progression to autoimmune disease	III
Kamen <i>et al</i> , 2008 <sup>74</sup>	472	To define the genetic and environmental factors contributing to SLE in the Gullah population	The severity of lupus in the Gullah population was similar to that in other African-American populations, whereas skin disease and familial disease prevalence were increased in the Gullah.	Findings suggest that there is an increased genetic influence on overall disease in this cohort compared with that in other African-American cohorts, which confirms the unique nature of this cohort	III
Lodolce <i>et al</i> , 2010 <sup>75</sup>	513	To examine two non-synonymous coding polymorphisms in the deubiquitinating domain of TNFAIP3: F127C, which is in high-linkage disequilibrium with reported SLE-risk variants, and A125 V, which has not been previously studied	Authors discovered a new African-derived risk haplotype that is separate from previously reported risk variants (OR 1.6, p=0.006), along with a rare protective haplotype defined by A125V (OR 0.31, p=0.027).	This is the first report of an association between <i>TNFAIP3</i> polymorphisms and autoimmunity in African-Americans	III

SLE, systemic lupus erythematosus.



and female first-degree relatives and male and female control subjects in this cohort had similar rates of ANA positivity. Authors concluded that the severity of lupus in the Gullah population is similar to that in other African-American populations, whereas skin disease and familial disease prevalence are increased in the Gullah, suggesting that there is an increased genetic influence on overall disease in this cohort compared with that in other African-American cohorts.

Since genome-wide association studies have implicated the TNF- $\alpha$ -induced protein 3 (TNFAIP3) locus in susceptibility to SLE in European cohorts, Lodolce *et al* conducted a case-control study in 513 African-American patients<sup>75</sup> with SLE using two non-synonymous coding polymorphisms (NCPs) in the deubiquitinating (DUB) domain of TNFAIP3: F127C, which is in high-linkage disequilibrium with reported SLE-risk variants, and A125V, which has not been previously studied. Authors tested the functional activity of the TNFAIP3 NCPs and found that the A125V coding-change variant altered the DUB activity of the protein to a greater extent than F127C. Authors identified a novel African-derived risk haplotype that is distinct from previously reported risk variants, along with a rare protective haplotype associated with A125V, making this the first report of an association between TNFAIP3 polymorphisms and autoimmunity in African-Americans.

### Quality of life

Most often in patients with SLE their HRQOL or the patient's perspective of how their health affects their function is poor, but few HRQOL studies in patients with SLE have focused on African-Americans despite an increased disease burden compared with Caucasians. We identified five studies that examined HRQOL in African-Americans with SLE (table 8).

Barnado *et al*<sup>76</sup> conducted a case-control study among a cohort of 89 SLE cases and 37 related controls from the African-American Gullah population of South Carolina. Authors measured demographics, medical history and short-form 36 (SF-36) and found that compared with related controls cases had a lower physical component summary (PCS), but not mental component summary (MCS). None of the 11 SLE ACR criteria, disease duration or SDI was associated with either PCS or MCS. Authors concluded that since cases and controls had similar MCS scores the lack of effect of SLE on MCS could be due to disease-coping mechanisms interplaying with cultural factors unique to the Gullah.

Barnado *et al*<sup>77</sup> performed a case-control study to test whether there is a predisease state that negatively affects pregnancy outcomes in Gullah African-Americans, comparing pregnancy outcomes before and after SLE diagnosis to controls. In total, 89 cases and 37 related controls, reporting at least one pregnancy, were included, and authors collected demographic, socioeconomic and pregnancy data. Authors observed that, compared with controls, cases were more likely to have

any adverse outcome, including stillbirth, spontaneous abortion, preterm birth, low birth weight and pre-eclampsia, and the odds of adverse pregnancy outcomes all increased after SLE diagnosis compared with before diagnosis. They concluded that there may be a predisease state in African-American women that predisposes them to adverse pregnancy outcomes.

Woods-Giscombe<sup>78</sup> conducted a qualitative study to develop a preliminary conceptual framework for superwoman schema (SWS) by exploring women's descriptions of the superwoman role; perceptions of contextual factors, benefits and liabilities; and beliefs regarding how it influences health, including adverse birth outcomes, lupus, obesity and untreated depression, since disparities in these areas have been explained by stress and coping and the strong black woman/superwoman role has been highlighted as a phenomenon influencing African-American women's experiences and reports of stress. Authors analysed eight focus group discussions with 48 demographically diverse African-American women and identified themes characterising the superwoman role and personal or sociohistorical contextual factors. Participants reported that the superwoman role had liabilities (relationship strain, stress-related health behaviours and stress embodiment), but also benefits (preservation of self and family or community), and authors concluded that the SWS framework could be used to enhance future research on stress and African-American women's health.

In a cross-sectional study of 578 African-American women participating in the Georgians Organized Against Lupus project, Chae *et al*<sup>79</sup> examined associations between unfair treatment, attributions of unfair treatment to racial discrimination and cumulative disease damage among African-American women with SLE. After controlling for demographic, socioeconomic and health-related factors in multivariate regression models, authors found that reporting any unfair treatment was associated with greater SLE damage compared with reporting no unfair treatment ( $b=0.55$ ; 95% CI 0.14 to 0.97). Although the association did not reach statistical significance, unfair treatment in general was found to be more strongly associated with SLE damage than unfair treatment attributed to racial discrimination. Authors concluded that unfair treatment appears to contribute to worse disease outcomes among African-American women with SLE, but that unfair treatment attributed to non-racial causes may have more detrimental effects on SLE damage.

In another expert opinion piece, Wallace<sup>80</sup> positions elevated rates of SLE in African-American women in the context of 'immune cognition' and suggests that the disease, for these women, is a physical manifestation of patterns of stress, discrimination and social disadvantage. Wallace introduces concepts of punctuated equilibrium in evolutionary theory and interactions within cognitive physiological submodules to explain how disease onset and progression, in this group, are guided by cognitive cues that are translated into physiological responses that

**Table 8** Five studies of quality of life in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Barnado <i>et al</i> , 2012 <sup>76</sup>	126	To study health-related quality of life in African-American patients with SLE from the Gullah population of South Carolina, which has a homogeneous genetic and environmental background and high prevalence of multipatient families with SLE	Cases had a lower PCS (41.8 vs 52.3, $p < 0.01$ ), but not MCS (55.0 vs 56.0, $p = 0.70$ ) compared with related controls. None of the 11 SLE American College of Rheumatology criteria, disease duration or Systemic Lupus International Collaborating Clinics Damage Index was associated with either PCS or MCS.	The lack of effect of SLE on MCS may be due to disease-coping mechanisms interplaying with cultural factors unique to the Gullah	III
Barnado <i>et al</i> , 2014 <sup>77</sup>	126	To compare pregnancy outcomes before and after SLE diagnosis to controls to test whether there is a predisease state that negatively affects pregnancy outcomes	The odds of adverse pregnancy outcomes all increased after SLE diagnosis compared with before diagnosis, even after adjustment for age, years of education, pregnancy number and medical coverage.	There may be a predisease state that predisposes to adverse pregnancy outcomes	III
Woods-Giscombé <i>et al</i> , 2010 <sup>78</sup>	48	To develop a preliminary conceptual framework for SWS by exploring women's descriptions of the superwoman role; perceptions of contextual factors, benefits and liabilities; and beliefs regarding how it influences health	According to the women in this study, the superwoman role involves sociohistorical and personal contextual factors as well as themes of survival and health status.	The SWS framework might be used to enhance future research on stress and African-American women's health	III
Chae <i>et al</i> , 2015 <sup>79</sup>	578	To examine associations between unfair treatment and disease damage among African-American women with SLE	Reporting any unfair treatment was associated with greater SLE damage compared with reporting no unfair treatment.	Unfair treatment contributes to worse disease outcomes among African-American women with SLE, and unfair treatment attributed to non-racial causes may have more detrimental effects on SLE damage	IV
Wallace, 2003 <sup>80</sup>	N/A	To examine elevated rates of SLE in African-American women in the context of immune cognition	Disease is an internalised physiological image of external patterns of structured psychosocial stress, discrimination and social disintegration experienced by ethnic minorities in the USA.	Social and economic reform necessary to decrease disease among African-American women will significantly benefit all groups	V

MCS, mental component summary; PCS, physical component summary; SLE, systemic lupus erythematosus; SWS, superwoman schema.

**Table 9** Two studies of race-tailored interventions in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Yuen <i>et al</i> , 2011 <sup>81</sup>	15	To evaluate the effectiveness of a home-based exercise programme among sedentary African-American women with SLE	Perceived fatigue severity was significantly decreased; body weight and waist circumference were significantly reduced; and anxiety level and overall intensity of total pain experience were significantly reduced.	Findings provide preliminary support that the Wii Fit programme motivates this population to exercise, which leads to reduced fatigue, body weight, waist circumference, anxiety level and pain intensity.	II
Yuen <i>et al</i> , 2013 <sup>82</sup>	14	To explore the process associated with the motivation for playing Wii Fit among patients with SLE	Authors found five themes (enjoyment, health benefits, sense of accomplishment, convenience and personalised) that revealed why the participants were motivated to play the Wii Fit. However, several participants commented they were not able to do many activities, master certain games or figure out how to play some; as a result, they were bored with the limited selection of activities that they could do.	The motivational elements of the Wii Fit may contribute to improved exercise motivation and adherence in select sedentary African-American women with SLE. Results provide a better understanding on the important elements to incorporate in the development of sustainable home-based exercise programmes with interactive health video games for this population.	III

SLE, systemic lupus erythematosus.

move African-American women from a 'normal' immune self-image to a self-attacking 'excited' state. He concludes that the social and economic reform necessary to decrease disease rates in African-American women would significantly benefit all groups.

### Race-tailored interventions

We identified two studies examining race-tailored interventions in African-Americans with SLE (table 9). Yuen *et al*<sup>81</sup> conducted a pilot intervention and evaluated the effectiveness of a home-based exercise programme using the Wii Fit system among 15 sedentary African-American women with SLE experiencing moderate-to-severe fatigue. Study participation included a home exercise programme, in which participants used a Wii Fit 3 days a week for 30 min each day for 10 weeks. A one-group pre-test–post-test design was used to evaluate the effectiveness of the programme. Severity of fatigue was the primary outcome measure. Other variables assessed included body weight, waist circumference, physical fitness, activity level and fatigue-related symptoms of distress. At the completion of the 10-week Wii Fit exercise programme, authors found that perceived fatigue severity was significantly decreased, and body weight and waist circumference were significantly reduced. In addition, overall intensity of total pain experience and anxiety level were also significantly reduced.

In a related qualitative study, Yuen *et al*<sup>82</sup> conducted individual in-depth semistructured telephone interviews

with 14 sedentary African-American women with SLE to explore their experiences and reflect on their motivation for playing Wii Fit after completing a 10-week home-based Wii Fit exercise programme. In a typical fashion of home-based exercise trials, in addition to the two themes (not wanting to let anyone down, and the ethical principle of keeping a commitment), authors identified five themes (enjoyment, health benefits, sense of accomplishment, convenience and personalised) that explained why African-American participants with SLE were motivated to play the Wii Fit. The enjoyment theme had three subthemes: competitive, challenging and interactive with an embedded social element. However, several participants commented they were bored with the limited selection of activities because they were not able to master certain games and could not figure out how to play others. Authors concluded that the motivational elements of the Wii Fit may contribute to improved exercise motivation and adherence in select sedentary African-American women with SLE, and their results provide a better understanding of the important elements to incorporate in the development of sustainable home-based exercise programmes with interactive health video games for this population.

### Self-management

We identified five recent studies that assessed the effectiveness of self-management programmes in reducing disease indices and complications in a total of 409

**Table 10** Five studies of self-management in African-Americans with lupus

Author, year	N	Objective	Results	Conclusions	Level of evidence
Drenkard <i>et al</i> , 2012 <sup>87</sup>	49	To pilot test the benefits of the CDSMP in low-income African-American patients with SLE	Authors witnessed significant improvements post intervention in the short-form 36 physical health component summary (p=0.032); self-efficacy (p=0.035); and several self-management behaviours: cognitive symptoms management (p=0.036); communication with physicians (p=0.01); and treatment adherence (p=0.01).	The CDSMP is a promising intervention for low-income African-Americans with SLE	II
Williams <i>et al</i> , 2014 <sup>83</sup>	30	To examine the relationship between psychosocial stress and underlying biological mechanisms that influence disease activity and pathology in a high-risk group	African-American patients with SLE experienced significant improvements in depression, social/role activities limitations, health distress, fatigue, pain and lupus self-efficacy.	This intervention has the potential to reduce health problems and costs in a debilitating, management-intensive chronic disease in the population subset at highest risk for the disease and should be more widely implemented and studied to more rigorously assess benefits	II
Williams <i>et al</i> , 2014 <sup>84</sup>	30	To link available disease information to endpoints examined in the cohort of 30 African-American lupus patients who participated in the BLESS study	Authors observed better outcomes in the intervention group following CDSMP workshops compared with the control group in the following areas: self-reported lupus flares, overall disease activity during the past 3 months, muscle pain and pain or stiffness in joints. Levels of reported stress had strong effects upon functionality, especially between health distress and functionality.	If widely implemented, morbidities and mortality related to lupus could be drastically reduced in African-Americans	III
Williams <i>et al</i> , 2014 <sup>85</sup>	30	To investigate relationships between stress, depression and various health behaviours in the cohort of 30 African-American lupus patients who participated in the BLESS study	Depressive symptoms had moderate effects upon social/role limitations and nights spent in the hospital.	Findings could have implications for developing interventions to improve disease experience and quality of life in African-American patients with SLE struggling with stress and/or depression	III
Williams <i>et al</i> , 2014 <sup>86</sup>	330	To characterise those who fully participated in the BLESS study and those who were non-compliant or non-responsive to recruitment attempts	Respondents and non-respondents to the BLESS study were similar with regard to demographic factors and disease indices, but study participants more quickly arrived at disease manifestations of renal disorder, haem disorder, and SLE diagnosis compared with non-respondents.	This information can be used to develop and refine future intervention activities	III

BLESS, Balancing Lupus Experiences with Stress Strategies; CDSMP, Chronic Disease Self-Management Program; SLE, systemic lupus erythematosus.



African-Americans with SLE (table 10).<sup>83–87</sup> The follow-up reported varied from 6 weeks to 6 months. The Chronic Disease Self-Management Program (CDSMP) was the mode of self-management education/implementation reported by each study; however, some studies also used electronic administrative records and disease activity data from medical histories, physical examination, phlebotomy and urine collection to assess changes.<sup>84 86 88</sup> Effects on the following risk factors were examined: gender, age, insurance status, highest year of education completed, current and past employment status, health status, self-efficacy, healthcare use, depression, social/role activities limitations, health distress, fatigue, pain, hospital visits, illness intrusiveness, communication with healthcare providers, perceived racism, neuroendocrine responses to stress (cortisol and dehydroepiandrosterone (DHEA)) and self-management behaviours.<sup>83–87</sup>

Drenkard *et al*<sup>87</sup> pilot tested the benefits of the CDSMP in 49 low-income African-American women with SLE who received medical care at a public lupus clinic in Atlanta, Georgia, USA. After delivery of CDSMP workshops, authors compared pre–post CDSMP changes (from baseline to 4 months after the start of the intervention) in health status, self-efficacy and self-management behaviours using self-reported measures. Authors also assessed healthcare use changes using electronic administrative records in the 6-month periods before and after the intervention. They observed significant improvements post intervention in the SF-36 physical health component summary, self-efficacy and several self-management behaviours, including cognitive symptoms management, communication with physicians and treatment adherence. The median number of outpatient visits decreased from 3 to 1, and authors concluded that the CDSMP intervention is promising for low-income African-Americans with SLE.

Williams *et al*<sup>83</sup> also piloted the validated ‘Better Choices, Better Health’ CDSMP in 30 African-American patients with lupus participating in the SLE Clinic Database Project at the Medical University of South Carolina (MUSC) to examine the relationship between psychosocial stress and underlying biological mechanisms that influence disease activity and pathology in this high-risk group. As part of the Balancing Lupus Experiences with Stress Strategies (BLESS) study, measures of psychosocial and biological indicators of stress were collected in all of the patients in each of the study conditions (15 intervention and 15 control) before and after intervention activities (from baseline to 6 weeks after the start of the intervention), as well as 4 months post intervention, to assess the effectiveness of the programme in reducing perceived and biological indicators of stress. Psychosocial indicators of stress were assessed by five validated measures: the State-Trait Anxiety Inventory, (the Arthritis Self-Efficacy Scale pain and other symptoms subscale, the Perceptions of Racism Scale, a modified version of the Medical Outcomes Study (MOS) health distress scale,

adapted by the Stanford Patient Education Research Center, and the Beck Depression Inventory. Quality of life was assessed using two instruments that describe a spectrum of quality-of-life outcomes; the Lupus Quality of Life Questionnaire (LUP-QOL), which incorporates the MOS SF-36 Health Survey and the Functional Assessment of Chronic Illness Therapy-Fatigue). Behaviour change was assessed using Stanford Patient Education Research Center Questionnaires assessing medical outcomes such as hospital visits, illness intrusiveness and communication with healthcare providers, healthcare use and use of stress management techniques. Biological indicators of stress were measured as salivary levels of cortisol and DHEA. Participation in the workshops had large effects on depression, fatigue, pain, health distress, social/role activities limitations and lupus self-efficacy. Authors concluded that the intervention workshops acted to reduce perceived stress and improve quality of life, implying that comparable, if not more, significant gains in relevant health indicators are possible in African-American patients with SLE when provided the opportunity to participate in CDSMPs.

In a related study, Williams *et al*<sup>84</sup> linked available disease information to end points examined in the cohort of 30 African-American patients with lupus in the SLE Clinic Database Project at the MUSC who participated in the BLESS Study. Disease activity data regularly assessed as part of the MUSC SLE Clinic Database Project included SLE Disease Activity Index and SLICC/ACR Damage Index scores. Disease activity data corresponding with BLESS study data collection timeframes for each participant were extracted from the MUSC SLE database to assess the effectiveness of the programme. Authors observed better outcomes in the intervention group following CDSMP workshops compared with the control group in the following areas: self-reported lupus flares, overall disease activity during the past 3 months, muscle pain and pain or stiffness in joints. Authors again concluded that such findings can be rapidly translated into improved delivery of healthcare and targeted trials/interventions with relevance to health disparities, and if widely implemented, morbidities and mortality related to lupus could be drastically reduced in African-Americans.

Williams *et al*<sup>85</sup> also conducted an exploratory study to investigate relationships between stress, depression and various health behaviours in the cohort of 30 African-American patients with lupus attending rheumatology clinics at MUSC who participated in the BLESS study. In their investigation of the association between anxiety/stress and functionality, authors observed that levels of reported stress had strong effects upon functionality, especially between health distress and functionality. In their investigation of the association between depressive symptoms and functionality, authors observed that depressive symptoms had moderate effects upon social/role limitations and nights spent in the hospital. Authors concluded that in addition to the significant reductions in stress and depression demonstrated by the

larger pilot project, this nested study showed that those improvements were positively associated with improved health behaviours and could have implications for developing interventions to improve disease experience and quality of life in African-American patients with SLE struggling with stress and/or depression.

Given that arthritis self-management education has reached a limited number of people and compliance is also a persistent problem in standardised programmes, Williams *et al*<sup>86</sup> examined predictors of non-response and non-compliance among 330 African-American patients with lupus participating in the MUSC SLE database whose recruitment attempts were made for the BLESS study. In order to characterise patients who participated completely in the study, and those who either did not respond to recruitment attempts or who were non-compliant, authors analysed data on 30 participants at baseline, 25 patients at post intervention (12 intervention and 13 controls) and 22 patients at 4 months post intervention (10 intervention and 12 controls), as well as the 300 remaining eligible African-American patients participating in the SLE Clinic Database Project. Patient background information, including gender, age, insurance status, highest year of education completed and current and past employment status, was included in the analysis. Disease factors considered included malar rash, discoid rash, photosensitivity, oral/nasal ulcers, arthritis, serositis, renal disorder, neuro disorder, haem disorder, immune disorder and ANA positivity, along with time to the onset of renal disorder, haem disorder and SLE diagnosis. Authors found that respondents ( $n=30$ ) and non-respondents ( $n=303$ ) to the BLESS study were generally similar with regard to demographic factors and disease indices, suggesting that factors outside of those related to disease and socioeconomic status may be more significant predictors of non-adherence and non-compliance. However, authors did observe some trends that could have implications for the development and implementation of future interventions. Their finding that study participants more quickly arrived at disease manifestations of renal disorder, haem disorder and SLE diagnosis, compared with non-respondents to recruitment efforts, suggests that more rapid onset of SLE may be more motivating than a more insidious onset and special efforts may have to be made to recruit those with later onset SLE. Additionally, findings of more rapid onset of haem disorder in study participants suggest that they were more fatigued at baseline compared with non-respondents. Authors concluded that this information can be used to develop and refine future intervention activities.

## CONCLUSIONS

Almost all articles included in our review correlated adverse outcomes in African-American patients with SLE with risk factors observed in other mono and multi-ethnic investigations. As previously noted in other

studies,<sup>21 89–91</sup> hypertension, higher creatinine, proliferative nephritis and decreased GFR,<sup>49 50</sup> as well as genetic, environmental and socioeconomic factors,<sup>50 92</sup> were associated with ESRD requiring dialysis. Similarly, even when studied separately, African-Americans with SLE continue to display chronic disease risk factors known for the general population (ie, smoking, hypertension, high LDL-c, etc) more frequently,<sup>58–60</sup> as observed in other investigations.<sup>93 94</sup>

Of interest, some of the studies limited to African-Americans with SLE identified novel methods for more precise ascertainment of risk and observed novel findings that had not been previously reported in African-Americans with SLE. Such findings included relationships between vitamin D levels and telomere length or cellular ageing that point to a promising biomarker of SLE status and disease activity in African-American patients with SLE<sup>56</sup> and the identification of features characteristic of the African-American scalp.<sup>57</sup> Studies of environmental impacts on disease included in this report employed CBPR and qualitative methods, as well as more meticulous collection of chemical exposure data that could ultimately lead to novel SLE-related autoimmunity prediction tools, to capture the complexity of the African-American lupus experience.<sup>51–53 56</sup> Other studies have also adopted innovative strategies for documenting exposure–outcome relationships in predominantly African-American populations, including exposure assessment according to the operation of a site of concern identified by community members and use of the arts to translate scientific findings in a community setting.<sup>95 96</sup>

Both environmental and genetic studies included in this review have highlighted unique African-American populations in an attempt to isolate risk attributable to African ancestry and observed increased genetic influence on overall disease in this cohort compared with that in other African-American cohorts and significant environmental differences that may impact progression to autoimmune disease.<sup>55 74</sup> In support of the claim that distinctive African genotypes that effect the risk of SLE have been maintained in the African-American population suggested by previous studies,<sup>97–99</sup> investigations included in this review identified new associations and specific risk loci<sup>63–69 73 75</sup> similar to discoveries reported in previous studies of specific genetic linkages to risk.<sup>100–107</sup> The high frequency of these alleles in African-Americans with near absence in European Americans explains an important proportion of the increased risk in African-Americans, expanding the knowledge and importance of these areas in the pathogenesis of lupus in the high-risk African-American population, and possibly even providing new targets for therapy and cure.

This review also revealed emerging research in areas of quality of life, race-tailored interventions and self-management. These findings included:

- discussions of specific predispose states that may predispose to adverse outcomes;<sup>77</sup>

- ▶ factors that impact motivation to participate in intervention programmes;<sup>82</sup>
- ▶ the interplay of disease-coping mechanisms with cultural factors unique to African-Americans.<sup>76 78</sup>

Findings of improved health outcomes following race-tailored interventions<sup>81 83 84 87</sup> were similar to the reported acceptability and effectiveness of other culturally specific intervention programmes<sup>108</sup> and consistent with studies that have suggested ways to neutralise, at least partially, the disadvantages of lower socioeconomic status associated with the excess morbidity and mortality in African-Americans with SLE.<sup>45 109 110</sup> These include:

- ▶ improving access to quality healthcare;
- ▶ targeting educational programmes to promote recognition and understanding of the disease and the comorbid conditions that affect outcome;
- ▶ implementing programmes to improve self-monitoring and adherence to medical regimens;
- ▶ developing opportunities to facilitate homemaking, childrearing and working outside the home;
- ▶ applying psychosocial interventions to enhance self-confidence and social support.

Self-management programmes in particular have demonstrated significant improvements in health distress, self-reported global health and activity limitation, with trends towards improvement in self-efficacy and mental stress management around the world<sup>111–117</sup> and in solely African-American populations with lupus<sup>81 83 84 87</sup> and may be one of the most promising areas of quality-of-life intervention. Findings can be rapidly translated into improved delivery of healthcare and targeted trials/interventions with relevance to health disparities. If widely implemented, morbidities and mortality related to lupus could be drastically reduced in African-Americans.

Potential limitations are those that threaten any literature review and include limitations at both the study and outcome level (eg, risk of bias) and at review level. There is the possibility that articles were missed by excluding articles based on title (or the other criteria), but efforts were made to ensure that keyword searches were as robust as possible and articles were not excluded on the basis of title alone. Each document was reviewed by two researchers in accordance with inclusion and exclusion criteria and followed up by the librarian on our authorship team to ensure that key articles were not missed. Any disagreements were submitted to a third researcher for final decision of inclusion or exclusion. This review may also be limited by our impartial summary of the findings. We did not discuss potential flaws in the evidence, but rather chose to focus on the breadth of literature specifically focused on African-Americans with SLE. While we recognise that comparing blacks with other racial/ethnic groups can provide insightful data regarding biological and environmental roots of the burden of SLE in the African-American population, it is well documented in published research that people of the African diaspora are significantly different than other communities in a number of diseases. Therefore, it is reasonable to focus

on within group differences. This review is meant to complement previous work. Our findings echo trends observed in the wealth of studies that have contributed to a better understanding of SLE in African-Americans,<sup>118–123</sup> and builds from that documentation for a deeper understanding of prevalence and clinical course in an effort to move towards better treatments and interventions for people of the African diaspora.

This review reemphasises the importance of additional studies to better elucidate the natural history of SLE in African-Americans and optimise therapeutic strategies for those who are identified as being at high risk. It introduces the possibility that comparable, if not more significant, gains in relevant health indicators are possible in African-American patients with SLE when provided the opportunity.

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