Doctopic: Analysis and Interpretation
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Cardiovascular risk in young people with childhood onset systemic lupus erythematosus

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Since 1940, epidemiologists, clinicians, and scientists promoted increased awareness of the crucial importance of promoting preventive strategies for minimising the risk of poor health later in life. This is particularly relevant to children and young people with chronic inflammatory diseases, including childhood-onset systemic lupus erythematosus (SLE), which are almost always associated with increased risk of comorbidity. A wealth of literature emphasises the contribution of chronic inflammation to the development of subclinical atherosclerosis, which drives the increased risk of cardiovascular disease, and many guidelines across specialties highlight the need for cardiovascular disease risk stratification and tailored management.

Childhood-onset SLE is a prototypical multisystem autoimmune rheumatic disease that is associated with increased cardiovascular risk due to various factors, which subsequently pose challenges in estimating and managing this risk. Childhood-onset SLE is known to be more severe than adult-onset SLE, and carries a significantly higher risk of cardiovascular disease than in children and young people in the general population. A large study from the UK reported a 4% prevalence of cardiovascular events in children and young people with childhood-onset SLE after less than 4 years of follow-up.[1] These events occurred at a median age of 16 years and only 2 years post-diagnosis. A Dutch study with a long follow-up into adulthood reported damage affecting the cardiovascular domain in 10·6% patients with childhood-onset SLE after a median disease duration of 20 years.[2] These findings highlight the need for improved cardiovascular disease risk management in childhood-onset SLE for improved outcomes[3].

The APPLE study,[4] a large interventional clinical trial, assessed the efficacy of atorvastatin in decreasing atherosclerosis progression in children and young people aged 10–18 years with childhood-onset SLE using serial carotid intima-media thickness (CIMT) measurements. The investigators estimated a higher rate of CIMT progression in these patients than that in patients with familial hypercholesterolaemia,[4] a condition associated with one of the highest cardiovascular disease risks in children and young people. Although the APPLE trial did not meet its primary endpoint, selected CIMT measurements and subgroup analysis suggested potential benefit from statins versus placebo in reducing CIMT progression over 3 years in patients with childhood-onset SLE.[5] Further analysis revealed significant heterogeneity in subclinical atherosclerosis at enrolment[6] and distinct patterns of CIMT progression in both the untreated and statin-treated groups. When using cardiovascular disease risk scores validated for use in general population across age, or other routinely available assessments of cardiovascular disease risk, children and young people with childhood-onset SLE and high CIMT progression rate were not correctly identified in the untreated group.[6] These observations highlight limitations of current standard practice in minimising cardiovascular risk in patients with childhood-onset SLE and the difficulty faced in identifying and managing children and young people with high risk of cardiovascular disease.[3]

To help prioritise this unmet need, we surveyed the international paediatric rheumatology community, aiming to explore their opinions about cardiovascular disease risk assessment of children and young people in the general population and in patients with childhood-onset SLE. We also asked the respondents for their preferred cardiovascular disease risk management choices for children and young people with childhood-onset SLE.

After consultation with patient representatives and childhood-onset SLE experts, a 17-question survey, endorsed by the Paediatric Rheumatology European Society (PReS) childhood-onset SLE Working Party and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Lupus Group, was disseminated (following local ethical approval) to the PReS and CARRA membership lists in November, 2022, and March, 2023, respectively. Respondents rated each of the factors suggested for consideration when assessing and managing cardiovascular disease risk on a 5-point scale from 5 (very important) to 1 (unimportant). Findings were reported using descriptive statistics and geographical differences were assessed using Fisher's exact test. Two levels of agreement (good [above 80%] and moderate [70–80%]) were explored and statements that received less than 70% agreement were also highlighted, especially if there were

	All respondents (N=161)	Europe and Africa (PReS members; N=92)	USA, Canada, and Mexico (CARRA members; N=69)	p value (PReS *vs* CARRA)
Training and experience				
Fully trained in paediatric rheumatology	107 (67%)	56 (61%)	51 (74%)	0·09
Dually trained in paediatric and adult rheumatology	15 (9%)	11 (12%)	4 (6%)	0·27
Trainees	37 (23%)	25 (27%)	12 (17%)	0·19
Allied health professional	2 (1%)	0	2 (3%)	0·18
Experience (years of practice, including training)				
≤10	108 (67%)	66 (72%)	42 (61%)	0·18
>10	53 (33%)	26 (28%)	27 (39%)	0·18
Number of patients with childhood-onset SLE seen per month				
5–10	116 (72%)	69 (75%)	47 (68%)	0·38
>10	45 (28%)	23 (25%)	22 (32%)	0·38
Agreement with the following statements				
CYP with childhood-onset SLE have increased risk of CVD	157 (98%)	88 (96%)	69 (100%)	0·14
It is necessary to assess CVD risk in CYP with childhood-onset SLE	153 (95%)	87 (95%)	66 (96%)	>0·99
Using a validated CVD risk score in childhood-onset SLE will have clinical use	145 (90%)	80 (87%)	65 (94%)	0·18
Healthy CYP can have atherosclerosis	130 (81%)	69 (75%)	61 (88%)	**0·04**
CVD risk should be assessed annually in childhood-onset SLE	112 (70%)	67 (73%)	45 (65%)	0·31
Most important factors driving CVD risk in CYP in the general population				
Good agreement overall (>80%)				
Smoking	160 (99%)	91 (99%)	69 (100%)	>0·99
Previous CVD event (myocardial infarction, angina, stroke)	160 (99%)	90 (98%)	69 (100%)	0·51
BMI	153 (95%)	90 (98%)	63 (91%)	0·07
Systolic blood pressure (mmHg)	152 (94%)	87 (95%)	65 (94%)	>0·99
Family history of CVD events	151 (94%)	89 (97%)	62 (90%)	0·10
Diastolic blood pressure (mmHg)	149 (93%)	86 (93%)	63 (91%)	0·76
Level of physical activity or diet	149 (93%)	88 (96%)	61 (88%)	0·13
Blood pressure treatment	149 (93%)	84 (91%)	65 (94%)	0·56
Weight	148 (92%)	86 (93%)	62 (90%)	0·56
Cholesterol or HDL/cholesterol ratio	146 (91%)	87 (95%)	59 (86%)	0·06
Waist and hip circumference	146 (91%)	87 (95%)	59 (86%)	0·06
Statin treatment	146 (91%)	81 (88%)	65 (94%)	0·27
Regular steroid treatment	146 (91%)	84 (91%)	62 (90%)	0·79
Hyperglycaemia	145 (90%)	88 (96%)	57 (83%)	**0·0078**
Increased LDL-cholesterol	145 (90%)	82 (89%)	63 (91%)	0·79
Increased intima-media thickness on vascular scans	144 (89%)	85 (92%)	59 (86%)	0·20
Endothelial dysfunction (measured as flow mediated vasodilation) on vascular scans	140 (87%)	82 (89%)	58 (84%)	0·36
Total cholesterol	139 (86%)	85 (92%)	54 (78%)	**0·01**
Aspirin treatment	139 (86%)	80 (87%)	59 (86%)	0·82
Triglycerides	138 (86%)	77 (84%)	61 (88%)	0·50
HDL-cholesterol	133 (83%)	76 (83%)	57 (83%)	>0·99

(Table continues on next page)

	All respondents (N=161)	Europe and Africa (PReS members; N=92)	USA, Canada, and Mexico (CARRA members; N=69)	p value (PReS *vs* CARRA)
(Continued from previous page)				
Lack of agreement overall (<70%)				
Deprivation	106 (66%)	61 (66%)	45 (65%)	>0·99
Sex	91 (57%)	57 (62%)	34 (49%)	0·11
Stress related to education, family issues, or peer pressure	83 (52%)	55 (60%)	28 (41%)	**0·02**
Puberty stage	69 (43%)	40 (43%)	29 (42%)	0·87
Receiving antipsychotic medication	59 (37%)	31 (34%)	28 (41%)	0·41
Severe mental illness	48 (30%)	32 (35%)	16 (23%)	0·12
Previous migraines	40 (25%)	28 (30%)	12 (17%)	0·07
Most important factors driving CVD risk in young people with childhood-onset SLE in addition to the above				
Good agreement overall (>80%)				
Previous cardio-vascular manifestations in the context of childhood-onset SLE	159 (99%)	91 (99%)	68 (99%)	>0·99
Childhood-onset SLE severity overall	157 (98%)	90 (98%)	67 (97%)	>0·99
Previous history of thrombosis	157 (98%)	90 (98%)	67 (97%)	>0·99
Severe organ involvement (eg, CNS, renal, or cardiac)	154 (96%)	90 (98%)	64 (93%)	0·14
Antiphospholipid syndrome screening positive	151 (94%)	86 (93%)	65 (94%)	>0·99
Childhood-onset SLE cumulative damage	150 (93%)	88 (96%)	62 (90%)	0·21
Childhood-onset SLE duration	145 (90%)	85 (92%)	60 (87%)	0·29
Duration of treatment with steroid	143 (89%)	83 (90%)	60 (87%)	0·62
Cumulative steroid dose	141 (88%)	83 (90%)	58 (84%)	0·33
Compliance with medication (overall)	129 (80%)	75 (82%)	54 (78%)	0·69
Good agreement in one group (>80%)				
Age at disease onset	123 (76%)	75 (82%)	48 (70%)	0·09
Childhood-onset SLE activity at a certain time point	119 (74%)	75 (82%)	44 (64%)	**0·02**
Patient currently treated to an agreed clinical target	112 (69%)	74 (80%)	38 (55%)	**0·0009**
Lack of agreement overall (<70%)				
Treatment with hydroxychloroquine	95 (59%)	53 (58%)	42 (61%)	0·75
Most important strategies for CVD risk management in childhood-onset SLE				
Moderate agreement overall (>70%)				
Tight control of comorbidities (eg, diabetes, obesity, or hypertension)	120 (75%)	70 (76%)	50 (72%)	0·72
Increased physical activity	119 (74%)	70 (76%)	49 (71%)	0·47
Moderate agreement in one group (>70%)				
Tight control of childhood-onset SLE	118 (73%)	71 (77%)	47 (68%)	0·21
Diet	114 (71%)	69 (75%)	45 (65%)	0·22
Lack of agreement overall (<70%)				
Tapering steroids	100 (62%)	58 (63%)	42 (61%)	0·87
Use of statins	78 (48%)	44 (48%)	34 (49%)	0·87
Optimisation of hydroxychloroquine treatment dose or compliance	74 (46%)	48 (52%)	26 (38%)	0·08
Other lipid lowering therapies	55 (34%)	31 (34%)	24 (35%)	>0·99

Data are n (%). CYP were defined as younger than 30 years. p<0·05 was considered statistically significant. Agreement took into consideration rating of 1 or 2 out of 5 for importance for each item evaluated (very important and moderately important). CARRA=Childhood Arthritis and Rheumatology Research Alliance. CYP=children and young people. SLE=systemic lupus erythematosus. CVD=cardiovascular disease. PReS=Paediatric Rheumatology European Society.

CNS - central nervous system

Table

geographical differences.

Out of 170 respondents interested in completing the survey, 161 (95%) fulfilled the requirement of being actively involved in looking after patients with childhood-onset SLE: 100 (62%) of 161 were from Europe, 54 (34%) from North America, and seven (4%) from other continents. We grouped the respondents based on their PReS versus CARRA membership to account for geographical differences and enable powered comparisons (table).

107 (67%) of 161 respondents were fully trained paediatric rheumatologists, 15 (9%) had dual (adult and paediatric) training, 37 (23%) were paediatric rheumatology trainees, and two (1%) were allied health professionals. 157 (98%) agreed that children and young people with childhood-onset SLE have a higher risk of cardiovascular disease than do the general population and 153 (95%) agreed that cardiovascular disease risk assessment in childhood-onset SLE is needed. Despite 81 (50%) of 161 respondents having never used a cardiovascular disease risk score to assess their patients, 145 (90%) agreed that a validated cardiovascular disease risk assessment tool would have clinical usefulness, with an annual assessment being the most preferred option (112 [70%]).

61 (88%) of 69 CARRA members and 69 (75%) of 92 PReS members were aware that children and young people can have subclinical atherosclerosis, despite their young age (p=0·04). A higher proportion of PReS members rated hyperglycaemia (p=0·0078) and total cholesterol (p=0·01) as very important or moderately important despite good agreement overall (table). In addition, less than 70% of respondents agreed that other factors included in cardiovascular disease risk stratification tools[3] (such as socioeconomic deprivation, sex, puberty stage, presence of mental health conditions or use of antipsychotic medication, stress, and migraines) were important for cardiovascular disease risk assessment in children and young people, with some geographical differences (table).

Respondents agreed overall (>80%) on cardiovascular disease risk factors relevant in childhood-onset SLE, with smoking, previous cardiovascular disease-related and thrombotic events, childhood-onset SLE severity, positive antiphospholipid antibodies, and childhood-onset SLE damage and duration rated by more than 90% respondents as important and moderately important. Significant diverging trends were noted for the rating of age at onset, disease activity at a certain timepoint, and treatment to agreed target as important in managing cardiovascular disease risk in patients with childhood-onset SLE, with good agreement reached only for PReS members (table).

In the absence of specific guidelines for cardiovascular disease risk management in childhood-onset SLE,[7] it is not surprising that only moderate consensus was reached in acknowledging the importance of tight comorbidity management and increase in physical activity as potential cardiovascular disease risk strategies (table). Only PReS respondents reached moderate agreement on considering tight childhood-onset SLE control and diet as suitable cardiovascular disease-management options. Steroid tapering, hydroxychloroquine treatment, and use of statin and other lipid lowering strategies did not reach consensus, although a slightly higher proportion of PReS members recognised a role for hydroxychloroquine treatment optimisation as a good strategy than did CARRA members (p=0·08).

This worldwide survey investigating paediatric rheumatology community opinions about cardiovascular disease risk in childhood-onset SLE provided preliminary data to support future work in this field. Good agreement was achieved for strategies for both general and disease-specific cardiovascular disease risk assessment in children and young people, although uncertainty remains regarding the optimal approach for cardiovascular disease risk management in childhood-onset SLE.

The small but statistically significant geographical differences in recognising the importance of cholesterol and glucose levels as drivers of cardiovascular disease risk in childhood-onset SLE, despite good agreement overall, could be explained by the progress achieved in identifying novel and better performing lipid biomarkers relevant for cardiovascular disease risk stratification of children and young people in both general population and childhood-onset SLE.[8,9] These novel biomarkers will require global validation before inclusion in clinical practice for tailored cardiovascular disease risk assessment and management in patients with childhood-onset SLE. More PReS members also opted for patient and clinician agreement to a target for treatment in childhood-onset SLE as a strategy for improved cardiovascular risk management, perhaps reflecting the impact of published PReS-endorsed considerations for treat-to-target in childhood-onset SLE[10] on practice. Future research is needed to assess the effect

of a treat-to-target approach on cardiovascular disease risk related outcomes before investing in clinicians' education or recommending the wider implementation of this treatment strategy in patients with childhood-onset SLE.

The survey also highlighted a lack of agreement in recognising the importance of other factors that are frequently included in validated cardiovascular disease risk assessment tools for use in children and young people in the general population. Despite evidence supporting a significant male sex bias to cardiovascular disease risk and research showing a pro-atherogenic serum lipid profile in young men post-puberty,[8] sex and puberty stage were not rated overall as important in assessing the cardiovascular disease risk of an individual, which is aligned with observations that the effect of sex hormones on lipid profile is blunted in patients with childhood-onset SLE.[9] No consensus has been reached about the use of hydroxychloroquine as a strategy for cardiovascular disease risk management in childhood-onset SLE, despite well-recognised cardioprotective benefits associated with this treatment in adult-onset SLE, suggesting need for further education of the paediatric community.

Other factors, such as socioeconomic deprivation, stress, current or history of mental health conditions, and migraines (although recognised in many studies as contributors to cardiovascular disease risk in children and young people) did not reach the threshold for good agreement regarding their importance in appreciating the individual cardiovascular disease risk in this survey, and therefore, they require further exploration in patients with childhood-onset SLE.

To our knowledge, this is the first assessment of clinical practice related to cardiovascular disease risk assessment and management in childhood-onset SLE with a representative survey sample size, considering that childhood-onset SLE is usually managed in specialist tertiary centres. This survey highlighted the paucity of evidence supporting best cardiovascular disease risk management approach in childhood-onset SLE, leading to the limited ability of paediatric rheumatology providers to reach good agreement on preferred treatment strategies. Our findings demonstrate the need for better research and international initiatives to formally agree on an approach to cardiovascular disease risk monitoring and treatment in childhood-onset SLE.

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