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Routine first-trimester pre-eclampsia screening and maternal left ventricular geometry

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Contributions

What are the novel findings of this work?

A high screening risk for developing preterm pre-eclampsia (PE) in the first trimester is associated with an increased maternal left ventricular mass index compared to participants with a low screening risk.

What are the clinical implications of this work?

As left ventricular mass is an independent risk factor for cardiovascular disease, women identified as being at high risk of preterm pre-eclampsia may benefit from further measures to optimise life-long cardiovascular health.

ABSTRACT

Objective

Preeclampsia (PE) is a pregnancy complication associated with premature cardiovascular disease morbidity and mortality. PE is associated with adverse left ventricular (LV) remodeling in the peripartum and postpartum period - an independent risk factor for cardiovascular disease. However, it is unknown if adverse cardiac remodeling is evident in the first trimester in participants at high compared to low risk of PE.

Methods

This was a prospective cohort study of singleton pregnancies that underwent screening for preterm PE as part of their routine first-trimester ultrasound assessment at a tertiary center in London, UK, between February 2019 and March 2020 at 11+0 weeks' gestation through 13+6 weeks' gestation. Screening for preterm PE was performed using the Fetal Medicine Foundation algorithm. Participants with a screening risk of ≥1 in 50 for preterm PE were classified as high-risk and those with a screening risk of ≤1 in 500 were classified as low-risk. All participants underwent two-dimensional and M-mode transthoracic echocardiography.

Results

A total of 128 participants in the first trimester of pregnancy were included in the analysis, with 57 (44.5%) participants screened as low-risk and 71 (55.5%) participants high-risk for PE. The risk groups did not vary in maternal age and gestational age at assessment. Maternal body surface area (BSA) and body mass index (BMI) were significantly higher in the high-risk group (all $p<0.05$). The high-risk participants were significantly more likely to be Afro-Caribbean, nulliparous, have a history of hypertensive disease in pregnancy and a family history of cardiovascular disease (all $p<0.05$). In addition, mean arterial blood pressure ($p<0.001$), heart rate ($p<0.05$), left ventricular mass (130.06 g, 113.62–150.5 vs. 97.44 g, 81.68–114.16, $p<0.001$) and left ventricular mass index (72.87 $\pm$ 12.2 g/m^2 vs. 57.54 $\pm$ 12.72 g/m^2, $p<0.001$) were significantly higher in the high-risk group. Consequently, the high-risk group were more likely to have abnormal left ventricular geometry (37.1% vs. 7.1%, $p<0.001$).

Conclusions

Early echocardiographic assessment in participants at high-risk of preterm PE may unmask clinically healthy individuals who are at increased risk for future cardiovascular disease. Adverse cardiac remodeling in the first trimester of pregnancy may be an indicator of decreased cardiovascular reserve and subsequent dysfunctional cardiovascular adaptation in pregnancy.

INTRODUCTION

Preeclampsia (PE) is a medical condition that occurs during pregnancy. It is characterized by high blood pressure and damage to one or more organ systems. PE affects approximately 5-8% of pregnancies and is a leading cause of maternal and fetal morbidity and mortality[1]. The risk of developing PE increases in women who have a history of high blood pressure, PE in a previous pregnancy, obesity, diabetes, or renal disease. Other risk factors are maternal age over 35, multiple pregnancies, and family history of PE[2]. Evidence is growing that pregnancy places a significant strain on the maternal cardiovascular system that can lead to maladaptation and result in the clinical phenotype of PE[3].

The ASPRE trial introduced a first-trimester screening algorithm for preterm PE that combines placental with maternal cardiovascular factors to identify women at a high risk of uteroplacental dysfunction[4]. A clinical-effectiveness study demonstrated that prophylactic treatment with a daily dose of 150mg of aspirin in women at high risk of preterm PE reduced the incidence of preterm PE by 80%[4, 5]. This screening considers maternal factors that apply to the patient regardless of whether she is pregnant, such as age, ethnicity, obesity, cigarette smoking and comorbidities (e.g., chronic hypertension, diabetes, systemic lupus erythematosus, antiphospholipid syndrome), all of which are risk factors for cardiovascular disease[6, 7]. PE has also been positively associated with chronic hypertension, obesity, elevated lipids and cardiovascular disease (myocardial infarction before the age of 60 years)[8, 9]. This overlap of risk factors indicates that screening for PE is screening for cardiovascular health, rather than merely a screening for a pregnancy complication.

In normal pregnancy the left ventricular (LV) mass increases up to 50% until term[10]. LV hypertrophy is determined by LV mass (LVM), which is a risk factor for cardiovascular disease, including heart failure, atrial fibrillation, myocardial infarction, and stroke[11]. There is a continuous relation between LVM and cardiovascular event rate in the general population[12]. This study aimed to investigate LV geometry by LVM and LVM index (LVMI), which are risk factors for cardiovascular disease, between participants with a high vs. low screening risk for preterm PE in the first trimester.

METHODS

Population

This was a prospective cohort study of singleton pregnancies booked for routine first-trimester ultrasound assessment between February 2019 and March 2020 at 11+0 weeks' gestation through 13+6 weeks' gestation at St George's Hospitals NHS Foundation Trust, London, UK. Ethics approval for the study was given by the National Research Ethics Service ethics committee London–Brent (19/LO/0794). All participants were offered first trimester screening for preterm PE according to the Fetal Medicine Foundation algorithm which includes maternal factors, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI) and pregnancy-associated plasma protein-A (PAPP-A). It has been demonstrated previously that PAPP-A performs similarly to placental growth factor (PlGF) in preterm PE screening when applied in the clinical setting[13]. At the routine 11–13 week first trimester ultrasound scan, gestational age was calculated according to crown–rump length, and the MAP and UtA-PI and were assessed as stated by established protocols[14-16]. Those with a screening risk of ≥1 in 50 for preterm PE were classified as the high-risk group. Participants with a screening risk of ≤1 in 500 were recruited and classified as the low-risk group. Participants <18 years of age at booking, preexisting cardiac structural or functional abnormalities, multiple pregnancies, a major fetal anomaly at the time of the first-trimester screening and who were not capable of providing informed consent were excluded from the study.

Study protocol

All participants underwent transthoracic echocardiography at rest in the left lateral decubitus position using a GE Vivid E95 scanner. Two-dimensional, M-mode echocardiography was performed following the guidelines of the American Society of Echocardiography[17]. For each acquisition, three cardiac cycles of non-compressed data were stored in cine-loop format and analyzed off-line by one investigator (A.R.) on a dedicated workstation (EchoPAC version 202, GE Healthcare, Little Chalfont, United Kingdom). Using the two-dimensional parasternal long-axis view, the left ventricular end-diastolic and end-systolic diameters (LVEDd and LVESd, respectively, in mm), as well interventricular septum (IVSD, in mm) and the posterior wall thickness (PWT, in mm) were measured. LVM (g) was calculated using the equation: $0.8 \times (1.04 \times ([LVEDd + PWT + IVSD]^3 - LVEDd^3) + 0.6$ and indexed for BSA to obtain LVMI, and relative left ventricular wall thickness (RWT) was calculated as follows: $RWT = 2 \times PWT/LVEDd$.

The participants' cardiac geometry was defined according to the following mutually exclusive categories: normal geometry (LVMI ≤95 g/m^2 and RWT ≤0.42); concentric remodeling (≤95 g/m^2 and RWT >0.42); eccentric remodeling (LVMI (>95 g/m^2 and RWT ≤0.42); concentric hypertrophy (LVMI >95 g/m^2 and RWT >0.42). LVM was subdivided into the following groups: normal (66–150 g) and abnormal (>150 g) (mild increase [151–171 g], moderate increase [172–182 g], severe increase [>182 g]). LVMI was subdivided into the following groups: normal (44–88 g/m^2), abnormal (≥89 g/m^2) (mild increase [89–100 g/m^2], moderate increase [101–111 g/m^2], severe increase [>112 g/m^2]).

Statistical analysis

Variables were assessed for normality using the Shapiro-Wilk test and by visualizing their histograms. According to the data distribution, continuous data were compared using the Student's t-test or Mann-Whitney U test as appropriate, and expressed as mean ± SD or median and interquartile range (IQR). Categorical data are presented as number (%) and compared using the chi-square test or Fisher exact test as appropriate. Statistical significance was deemed a priori as p<0.05. All data were analyzed using the statistical package for social sciences (SPSS 29 release version for Windows; SPSS Inc., Chicago IL, USA).

RESULTS

Demographic and pregnancy characteristics

In total, 128 participants were recruited in the first trimester of pregnancy and included in the analysis, with 57 characterized as low-risk and 71 high-risk for PE. Demographic and pregnancy related characteristics of the study groups are displayed in Table 1. There was no significant difference between low and high-risk PE groups for maternal age, gestational age or height. However, the high risk for PE group had a significantly greater maternal BSA (m^2) at assessment, maternal weight (kg), and maternal BMI (kg/m^2). Afro-Caribbean ethnicity, first pregnancy, assisted reproduction, a family history of hypertensive disorder of pregnancy as well as other cardiovascular diseases were significantly greater in the high-risk group. In addition, mean arterial pressure (MAP) and heart rate (HR) were significantly greater in the high-risk for PE group at the first-trimester assessment (Table 1).

Left ventricular geometry in the first trimester

When individual markers of LV geometry were considered, IVSd (cm) (p<0.001), LV posterior wall thickness at the end of diastole (cm) (p<0.001), LVM (g) (p<0.001), LVMI (g/m^2) (p<0.001) and RWT (cm) (p<0.001) were all significantly greater in the high-risk group compared to the low-risk group. The index of the LV internal diameter at the end diastole (cm/m^2) was significantly (p<0.001) decreased in the high-risk compared to the low-risk group (Table 2 and Figure 1).

The differences in LV dimensions translated into the high-risk group having a significantly greater LVM (p=0.002), LVMI (p=0.014) and a significantly greater proportion with abnormal cardiac remodeling (p<0.001). A normal LVM was calculated in 54 (94.7%) participants in the low-risk group and 52 (74.3%) participants in the high-risk group (p=0.002). A mild increase in LVM was calculated in 3 (5.3%) participants in the low-risk group and 11 (15.7%) participants in the high-risk group (p=0.061). Three (4.3%) participants in the high-risk group had a moderate increase of LVM (p=0.114), and 4 (5.7%) participants had a severe increase of LVM (p=0.067). A normal LVMI was calculated in all low-risk participants and 63 (90%) participants in the high-risk group (p=0.014). A mild increase in LVMI was calculated in 6 (8.6%) participants in the high-risk group (p = 0.024), and 1 (1.4%) participant in the high-risk group had a moderate increase of LVMI (p=0.365). Normal LV geometry was calculated in 52 (92.9%) participants in the low-risk group and 44 (62.9%) participants in the high-risk group (p<0.001). Concentric remodeling was calculated in 4 (7.1%) participants in the low-risk

group and 21 (30%) participants in the high-risk group (p=0.001). Furthermore, one (1.4%) participant in the high-risk group showed eccentric remodeling (p=0.369), while four (5.7%) participants in the high-risk group had concentric hypertrophy (p=0.067). The results are summarized in Table 3.

DISCUSSION

This study demonstrates that participants with a high screening risk for preterm PE have a significantly increased LVM, LVMI and altered LV geometry compared to low-risk participants, which may impact short and long-term cardiovascular disease risks.

Cardiovascular disease is a global health issue and a leading cause of morbidity and mortality worldwide. LV geometric abnormalities are well-known independent risk factors for cardiovascular disease and is associated with PE at term[18]. Not only do PE and cardiovascular disease share the same risk factors, but pre-existing cardiovascular disease is also the strongest risk factor for developing preterm PE. Women with a history of preterm PE have a higher risk of developing hypertension, stroke, ischemic heart disease, and heart failure later in life compared to normal pregnancy. One study reported that women who had preterm PE had a 2.5-fold increased risk of developing hypertension, a 3.5-fold increased risk of ischemic heart disease, and a 1.7-fold increased risk of stroke compared to women who did not have PE[19].

As demonstrated by this study, women who have been screened as high risk for developing preterm PE show significant signs of cardiac alterations, as early as the first trimester of pregnancy. Although abnormal trophoblast invasion has been proposed as the cause of PE by poor placentation for the past 150 years, this study demonstrates that suboptimal cardiovascular adaptation may be associated with poor placentation. Uteroplacental malperfusion through primary maternal cardiovascular dysfunction may still lead to syncytiotrophoblast damage by ischemic injury, with consequent abnormal placental signaling and development of the systemic inflammatory response occurring as PE. In this study, 37.1% of participants in the high-risk group demonstrated adverse cardiac remodeling and/or hypertrophy, 25.7% showed an abnormally increased LVM and even after correcting for BSA, 10% still had a pathological increase during the first trimester of pregnancy. Most of these individuals were clinically healthy, young pregnant women. In the low-risk group only 7.1%, 5.3% and 0% of participants showed these changes in left ventricular geometry, LVM and LVMI, respectively.

Prior studies have shown the short term (4 to 7 years) adverse effect of LV hypertrophy; specifically, the strong relationship of LV hypertrophy and heart failure, with variable association with coronary artery disease related events[11, 20-22]. Another study with longer follow-up (15 years) revealed that LV hypertrophy was independently associated with both non–coronary-related and coronary-related cardiovascular events (myocardial infarction, coronary artery disease–related death), as well as heart failure. Cardiovascular death rate was 7.5 times greater in participants with LV hypertrophy than

in those without LV hypertrophy[23]. Increased LVM reflects diminished myocardial functional reserve due to a relative reduction in microvascular circulation/coronary flow reserve[24, 25]. LVM increase also occurs in athletes to adjust to the increased cardiovascular strain during exercise; however, there are several distinctions between exercise-induced LV changes compared with hypertensive/maladaptive LV hypertrophy. For example, HR remains unaffected in the hypertensive heart but is decreased in the athlete's heart [26]. In this study participants in the high-risk group had a significantly higher HR. Furthermore, female athletes who engage in regular high-intensity exercise may experience an increase in LVM due to the demands placed on the heart to meet the increased oxygen demands of the body during exercise. However, studies have shown that the degree of LVM increase in female athletes is generally modest and within the normal range for healthy individuals[27, 28].

Our results demonstrate that the inclusion of echocardiography during the screening process for preterm PE may unmask clinically healthy individuals who are at increased risk for cardiovascular disease. Therefore, these patients might benefit from preventative measures (such as maintenance of a healthy weight, exercise, diet, smoking cessation, blood pressure control, management of cholesterol levels, stress reduction) in order to reduce cardiovascular disease risk later in life. We hypothesize that the LV hypertrophy reported in the high-risk group in the first trimester of pregnancy before the peak "physiologic" volume overload of pregnancy occurs, may be an indicator of decreased cardiovascular capacity pre-pregnancy and dysfunctional cardiovascular adaptation in early pregnancy. One may even consider if the screening for preterm PE is in fact a screening for the individual patient's cardiovascular risk. The development of improved screening, treatment and diagnostic strategies will be stagnant until better understanding of the cardiovascular etiology of PE is widely accepted.

Strengths and limitations of work

One of the strengths of the study was its prospective longitudinal design, as the study design and strict protocol allowed us to control for confounders that might affect cardiovascular assessment. Furthermore, this study provided a thorough exam of LV geometry in clinically healthy pregnant women. Thus, the study gathered important information on the cardiac profile of women who have been screened as high risk for developing preterm PE and may help lay the groundwork for future studies on cardiovascular markers for predicting PE.

However, the small sample size did not enable us to draw conclusions about the value of the cardiovascular markers assessed in this study for predicting PE. In addition, more participants are necessary to conduct further subgroup analyses; for example, a longitudinal study about women at high risk for developing preterm PE could subdivide participants who do and do not develop diseases of the uteroplacental circulation. This might further help assess risk profiles in early pregnancy.

Conclusion

This study demonstrates that women with a high screening risk for preterm PE exhibit altered LV geometry and LVM/LVMI during the first trimester of pregnancy. These findings may have significant implications for the short and long-term cardiovascular health of these women. Early identification of cardiac maladaptation during pregnancy may identify women at high risk of preterm PE and allow timely implementation of preventative measures to reduce cardiovascular disease risk.

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FIGURE LEGENDS

Figure 1 Radar chart of important measurements of left ventricular geometry in the first trimester in the high-risk group (red) compared to the low-risk group (blue). IVSD, interventricular septum diameter; LVIDd, left ventricular internal diameter end diastole; LVIDdI, left ventricular internal diameter end diastole index; LVPW, left ventricular posterior wall end diastole; LVIDs, left ventricular internal diameter end systole; LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, relative wall thickness; * = $p < 0.05$

Table 1: Baseline characteristics in the risk groups at the recruitment assessment.

Baseline characteristics	Low-risk group (N = 57)	High-risk group (N = 71)	*p*-value
Maternal age (years)	32.5 ± 3.9	32.8 ± 5.1	0.681
Maternal weight (kg)	63.00 (59.00–70.50)	72.00 (63.20–87.70)	**< 0.0001**
Maternal height (cm)	166.3 ± 6.6	164.2 ± 6.6	0.072
Maternal BMI (kg/m^2)	23.00 (20.90–25.70)	27.60 (23.90–31.90)	**< 0.0001**
Maternal BSA (m^2)	1.70 (1.63–1.81)	1.79 (1.67–1.96)	**0.007**
Ethnicity			
Caucasian N (%)	51 (89.5)	44 (61.9)	**< 0.0001**
Asian N (%)	5 (7.0)	9 (12.7)	0.292
Afro-Caribbean N (%)	2 (3.5)	18 (25.4)	**0.001**
Conception			
Spontaneous N (%)	57 (100)	61 (85.9)	**0.003**
Assisted N (%)	0 (0)	10 (14.1)	
Family history of cardiovascular disease			
Hypertensive disease of pregnancy N (%)	4 (7)	15 (21.1)	**0.026**
Other cardiovascular disease N (%)	17 (29.8)	34 (47.9)	**0.038**
Gestational age at recruitment (weeks)	12.80 ± 0.62	12.60 ± 0.57	0.118
PAPP-A (mIU/mL)	2.942 (1.764–4.477)	1.548 (0.968–2.785)	**< 0.0001**
PAPP-A MoM	1.471 (0.888–1.908)	0.849 (0.536–1.291)	**< 0.0001**
Average uterine artery PI	1.210 (0.969–1.508)	1.825 (1.475–2.175)	**< 0.0001**
Mean arterial pressure (mmHg)	81.35 ± 6.51	96.30 ± 8.28	**< 0.0001**
Heart rate (bpm)	70.2 ± 8.7	78.4 ± 11.6	**< 0.0001**

Mann-Whitney-U test was applied to assess nonparametric values. Values are presented as medians with IQR. For normally distributed data, T-Tests were performed. The results are presented as median ± standard deviation (SD).

Table 2: Important measurements of left ventricular geometry in the first trimester, comparing high-risk and low-risk groups. Mann-Whitney-U test was applied to assess nonparametric values. Values are presented as medians with IQR. For normally distributed data, t-tests were performed. Values are presented as median ± standard deviation (SD)

First-trimester left ventricular geometry	**High-risk group (N = 71)**	**Low-risk group (N = 57)**	***p*-value**
Interventricular septum diameter (cm) (median (IQR))	0.90 (0.80–1.00)	0.60 (0.60–0.80)	**< 0.0001**
Left ventricular internal diameter end diastole (cm) (mean ± SD)	4.51 ± 0.42	4.59 ± 0.34	0.266
Left ventricular internal diameter end diastole index (cm/m^2) (mean ± SD)	2.49 ± 0.27	2.67 ± 0.26	**< 0.0001**
Left ventricular posterior wall end diastole (cm) (median (IQR))	0.90 (0.80–1.00)	0.70 (0.60–0.80)	**< 0.0001**
Left ventricular internal diameter end systole (cm) (median (IQR))	2.80 (2.60–3.15)	3.00 (2.80–3.30)	0.076
Left ventricular mass (g) (median (IQR))	130.06 (113.62–150.5)	97.44 (81.68–114.16)	**< 0.0001**
Left ventricular mass index (g/m^2) (mean ± SD)	72.87 ± 12.2	57.54 ± 12.72	**< 0.0001**
Relative wall thickness (cm) (median (IQR))	0.41 (0.37–0.46)	0.31 (0.27–0.35)	**< 0.0001**

Table 3: Qualitative assessment of left ventricular mass in the first trimester in low-risk versus high-risk groups. N (%)

	Low-risk group (N = 57) N (%)	High-risk group (N = 70) N (%)	***p*-value**
Left Ventricular Mass (g)			
Normal (66–150 g)	54 (94.7)	52 (74.3)	**0.002**
Abnormal (> 150 g)	3 (5.3)	18 (25.7)	
Left Ventricular Mass Index (g/m^2)			
Normal (44–88 g/m^2)	57 (100)	63 (90.0)	**0.014**
Abnormal (≥ 89 g/m^2)	0 (0)	7 (10.0)	
Left Ventricular Geometry			
Normal geometry	52 (92.9)	44 (62.9)	**< 0.001**
Abnormal geometry	4 (7.1)	26 (37.1)	
Concentric remodeling	4 (7.1)	21 (30)	**0.001**
Eccentric remodeling	0 (0)	1 (1.4)	0.369
Concentric hypertrophy	0 (0)	5 (5.7)	0.069

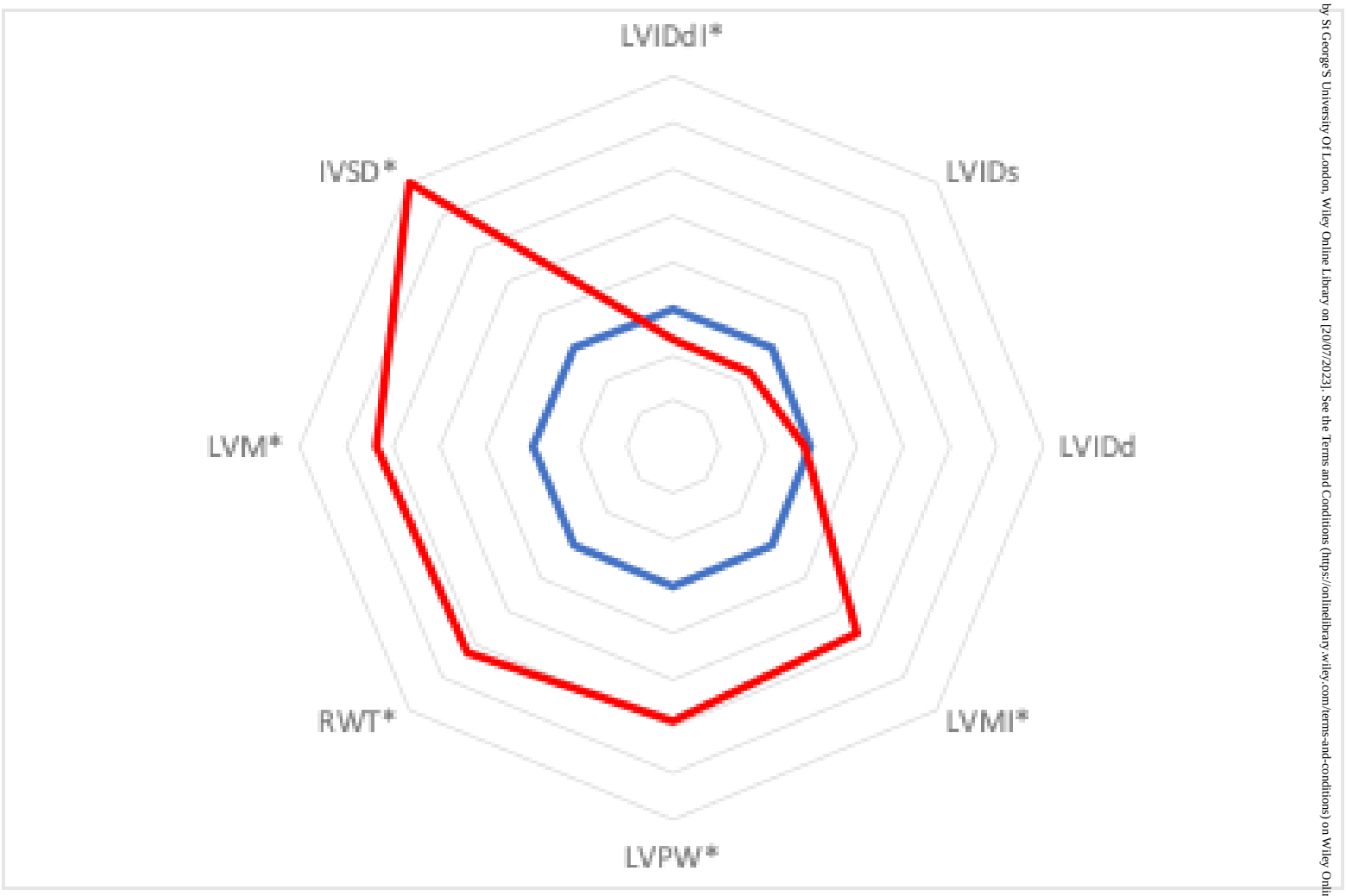

Figure 1.png