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# BMJ Open

## Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic review.

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6 2 **Title page**  
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14 5 **Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic**  
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16 6 **review.**  
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46 17 **Key words:** Endo-PAT 2000, peripheral artery tonometry, Endothelial dysfunction, paediatric  
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48 18 diabetes mellitus, chronic diseases  
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3 **23 Abstract:**  
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6 **24 Objectives:** Endo Peripheral Artery Tonometry (EndoPAT-2000) is a non-invasive technology for  
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8 **25** measuring endothelial dysfunction (ED). The reactive hyperaemia index (RHI) is resulted and is low  
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10 **26** when endothelial dysfunction is present. Microvascular ED, the early stage of atherosclerosis,  
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12 **27** precedes macrovascular ED and can be detected in children and adolescents.  
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15 **28 Design:**  
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18 **29** A comprehensive systematic review was conducted to identify publications that investigated the use  
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20 **30** of Endo-PAT 2000 from 2015 to present.  
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23 **31 Results:**  
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26 **32** 156 articles were identified in our review. We have subdivided these papers into different systems for  
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28 **33** ease of reference and have reported our findings in 6 tables.  
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31 **34 Conclusions:**  
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34 **35** A number of papers using Endo-PAT for children with various chronic diseases have evidence of ED.  
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36 **36** It should be concerning to paediatricians that children with various chronic diseases have evidence of  
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38 **37** ED. However, in many cases, there has only been a single cohort study using Endo-PAT. Further  
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40 **38** studies are required to validate these findings and to help characterise the cardiovascular risk profile  
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42 **39** of children with chronic disease. Further studies are also required that will characterise more  
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44 **40** completely the cardiovascular risk profile of these children with chronic disease.  
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47 **41** Consensus on other vascular risk markers that could be included in future studies is ideal and if  
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49 **42** accomplished, this would facilitate meta-analyses of studies of conditions with relatively rare  
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51 **43** conditions.  
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3 47 **Strengths and limitations:**  
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- 6 48 • Comprehensive literature review on paediatric endothelial dysfunction from 2015 to present.  
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8 49 • All study types were reviewed and even the studies without results but had interesting points  
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10 50 were included in our discussion.  
11  
12 51 • Awareness of ED in paediatric patients can aid an approach to cardiovascular risk assessment  
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14 52 for young children and adolescents, in particular those with chronic diseases.  
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16 53 • Separate paediatric results were obtained where possible from studies with combined adult  
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18 54 and paediatric data.  
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20 55 • Further studies would help characterise the cardiovascular risk profile of children with  
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22 56 chronic diseases.  
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30 59 **Introduction:**  
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33 60 Endothelial dysfunction (ED) is an early predictor of cardiovascular disease(1). ED occurs when the  
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35 61 endothelium loses its ability to promote vasodilation, fibrinolysis and anti-aggregation(2). It can be  
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37 62 caused by oxidative stress with loss of vaso-active or inflammatory homeostasis within the body's  
38  
39 63 vascular system. It may be secondary to mechanical stimuli, for example increased intraluminal  
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41 64 pressure within the blood vessel or metabolic factors such as hormones (oestrogen's vasodilation  
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43 65 action)(3). Damaged endothelium can release a cascade of substances which pose a risk of  
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45 66 thrombosis, inflammation and ultimately atherosclerosis(4).  
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48 67 ED in paediatric populations has been associated with several conditions including type 1 diabetes  
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50 68 (T1D), type 2 diabetes (T2D), renal impairment, obesity, metabolic syndrome, etc(5). ED can  
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52 69 progress to atherosclerosis which is a chronic condition that poses severe risk of coronary artery  
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54 70 disease, stroke, peripheral arterial disease, etc.  
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57 71 Improving glucose control can protect endothelial function. Persistent high sugars can impair  
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59 72 endothelial function via oxidative stress, free-radicals, etc(2). Diabetic microangiopathy can result in  
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3 73 the outcomes of retinopathy, neuropathy and peripheral vascular neuropathy. Subclinical evidence of  
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5 74 these complications can be seen in paediatric patients, especially in those with poor glycaemic  
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7 75 control. In patients with T2D, obesity and metabolic syndrome, insulin resistance is one of the most  
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9 76 importance factors contributing to ED(6). Metabolic syndrome is a pro-inflammatory state where  
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11 77 dyslipidaemia, hyperuricemia, and hypertension occur and can predispose to ED(7). Unfortunately,  
12  
13 78 there have been reports of T2D paediatric patients diagnosed with microangiopathic complications,  
14  
15 79 particularly nephropathy(8). This early endothelial damage can be linked with increased morbidity  
16  
17 80 and mortality(9). New onset diabetes after transplantation (NODAT) is characterised by insulin  
18  
19 81 resistance and T2D(10).  
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23 82 In recent decades, the number of childhood cancer survivors is increasing(11). Treatments utilized  
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25 83 such as haematopoietic stem cell transplantation have increased risk of cardiovascular disease(12, 13).  
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27 84 Following chemotherapy, radiotherapy, immunosuppressive treatments the risk of insulin resistance  
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29 85 has been noted(14). With advances in treating malignant paediatric conditions there are long term  
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31 86 complications emerging in survivors. High dose chemotherapy including anthracyclines, alkylating  
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33 87 agents and vinca alkaloids may disrupt the substances on the surface of the endothelium and impair its  
34  
35 88 ability to dilate and constrict. Moreover, total body radiation poses a risk by damaging the elastic  
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37 89 matrix. Heart disease in long-term cancer survivors is 5-10 times higher than their siblings(14).  
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#### 43 **Endo-PAT 2000:**

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46 92 Endo Peripheral Artery Tonometry (Endo-PAT 2000) is a non-invasive technology for measuring ED  
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48 93 developed by Itamar Ltd. Non-invasive pneumatic probes which are placed on the both index fingers,  
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50 94 which continuously records pulse wave amplitude. A blood pressure cuff is inflated to occlude blood  
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52 95 flow and response after deflation is recorded. The reactive hyperaemic index (RHI) is resulted  
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54 96 following this mini-ischemic stress to the vessel. The pulse wave amplitude (PWA) is measured and  
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56 97 computes a RHI result automatically. RHI is calculated as the ratio of average PWA divided by the  
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3 98 average amplitude during the equilibration period. To compensate for any systemic changes, this ratio  
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5 99 is normalized to a concurrent signal from the contralateral finger.  
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8 100 Numerous studies in both adult and paediatric literature reveal Endo-PAT's excellent reproducibility  
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10 101 and reliability(15, 16). In ED, the RHI is low and pulse amplitude is high. PAT also provides results  
11  
12 102 on the peripheral augmentation index (PAT-AIx). Bonetti et al report a RHI of <1.35 as indicative of  
13  
14 103 coronary ED in adults(17). However, there is no reported RHI cut off value in paediatric patients.  
15  
16 104 Endo-PAT can be used at the patient's bedside, without extensive training required of the operator.  
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19 105 Prior to Endo-PAT, ED had been assessed by flow-mediated vasodilation (FMD). FMD uses an  
20  
21 106 ultrasound to assess the change in brachial artery diameter in response to increased flow after a period  
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23 107 of vascular occlusion by a blood pressure cuff. A reduction in FMD represents ED. FMD is  
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25 108 technically challenging to perform, user-dependent and requires training. FMD results macro blood  
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27 109 vessel reactivity whereas Endo-PAT results micro, which may account for the challenges in  
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29 110 comparing the two techniques. Endo-PAT is easier to set up, is automated and less user-dependent.  
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### 32 111 **Objective:**

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35 112 The aim of this study is to conduct a systematic review of the use of Endo-PAT 2000 with particular  
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37 113 emphasis on paediatric populations.  
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### 41 115 **Methods:**

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44 116 A comprehensive systematic review was conducted to identify publications that investigated Endo-  
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46 117 PAT 2000. All papers published from 2015 to March 2021 in paediatric populations age birth to 16  
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48 118 years of age were analysed. PRIMSA study design was used.  
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51 119 The following scientific databases were searched: The Cochrane Database, MEDLINE EBSCO,  
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53 120 EMBASE (Ovid), PUBMED and CINAHL EBSCO. The search was not limited by language. The  
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55 121 search was limited by type of subjects (human), date (2015 to March 2021) and included all study  
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57 122 types. Snowballing method was used. Authors of joint adult and paediatric papers were contacted by  
58  
59 123 email to obtain separate paediatric data.  
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3 124 The database search was repeated several times using the combinations of keywords, MeSH terms and  
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5 125 filters (child: birth-16 years). The following MeSH terms or key words were used for searching:  
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7 126 Peripheral arterial tonometry, PAT test, endopat, adolescent, ado\*, child, paediatric, pediatric,  
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9 127 preschool, schoolboy, schoolgirl, boy, girl, teen, toddler, infant, baby.

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12 128 Exclusion criteria were: 1. If a study used a different device for example 'Watch-PAT; 2. If the study  
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14 129 had no results. Inclusion criteria were: 1. Published in the English; 2. More than 50% of study  
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16 130 subjects were in the paediatric age range; 3. Data relevant to paediatric age range children could be  
17  
18 131 extrapolated from all data, where not all study subjects were children. A child was defined as up to 16  
19  
20 132 years, and this is consistent with PubMed's definition of a child. Where data relevant to children  
21  
22 133 could not be extrapolated from the whole dataset, the study authors were contacted for additional  
23  
24 134 information prior to study inclusion or exclusion.

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28 135 **Patient and public involvement:**

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30 136 No patient involved.

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33 137 **Data collection and analysis:**

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36 138 A total of 290 articles were obtained via the online database search (*Figure 1*: flow diagram).  
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38 139 Following removal of duplicates, 158 articles remained. The second screening was conducted by  
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40 140 'Rayyan- systematic review software' Copyright © 2021 Rayyan. Two further duplicate articles were  
41  
42 141 removed, with 156 remaining for review.

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45 142 Two independent authors separately performed a blind screen on the 156 abstracts. 65 articles were  
46  
47 143 initially excluded based on title or abstract: 37 adult studies, 18 'PAT' did not represent peripheral  
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49 144 arterial tonometry (e.g. prism adaptation test, psychosocial assessment tool), 6 Watch-PAT, 2 sleep  
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51 145 studies and 2 had no results available.

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54 146 The remaining 91 articles were analysed viewing full text articles for further information. A further 20  
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56 147 were screened out as did not fit inclusion criteria or have results to report. Some of these articles that  
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58 148 included Endo-PAT 2000 in paediatrics were referenced in the discussion.

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3 149 Twenty-eight authors of studies including both adults and paediatric patients were contacted twice by  
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5 150 email to gather separate information on the paediatric participants. Twenty authors did not reply and  
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7 151 were thus excluded. Eight authors replied: three providing results, four unable to give separate  
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9 152 paediatric data and one author's research was on adult patients so was excluded. Three of the articles  
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11 153 whose authors replied with data were included in our review.

14 154 Four studies were obtained via snow balling searching. Some articles did not have results for the  
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16 155 systematic review but had reviews and conclusions that were relevant to the paper and so were  
17  
18 156 excluded from analysis.

21 157 A total of 50 articles were included in our results and are represented in tables 1-6. For each eligible  
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23 158 study the following data was reported: author, year of publication, design of the study, population  
24  
25 159 studied, control group (if available), RHI results.

28 160

## 31 161 Discussion

34 162 This literatures search identified 156 articles in the published paediatric literature on ED in children.

36 163 We have subdivided these papers into different systems for ease of reference (*Tables 1-5,*

38 164 *supplementary material, supplementary table 1*).

Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Adolescents and young adults with type 1 diabetes display a high prevalence of endothelial dysfunction. Scaramuzza et al (18)	2015	Cohort prospective observational study	n=73 T1D adolescents, diagnosed > 1 year, 16.2 $\pm$ 3.5 years, [F/M 25/48]	No controls. Results at baseline and after a 1-year follow-up	56 (76.7%) had ED, with lower mean RHI scores (1.26 $\pm$ 0.22 versus 2.24 $\pm$ 0.48, p < 0.0001). More with ED had abnormal cardiac autonomic tests (p = 0.02) and were more sedentary. After 1 year follow-up in 64/73 patients, 81.8% had ED, despite some improvement in	T1D adolescents had evidence of ED. Good metabolic control (HbA1c $\leq$ 7.5%) and regular physical activity might be protective. ED progression despite some improvement to HbA1c.

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					HbA1c. ED rate recorded at baseline was 76.7%.	
Alpha-Lipoic Acid and Antioxidant Diet Help to Improve Endothelial Dysfunction in Adolescents with Type 1 Diabetes: A Pilot Trial. Scaramuzza et al (19)	2015	Double-blind, randomized controlled trial – snow balling	n=71 T1D patients, followed for at least 1 year, age $16.3 \pm 3.4$ years, [F/M 29/42]	Results at baseline and after follow-up.	3 double-blind study arms: 10,000 ORAC antioxidant diet +/- lipoic acid: RHI $1.40 \pm 0.68$ vs $1.72 \pm 0.66$ ( $P < 0.05$ ) (baseline vs after 6 months). 10,000 ORAC antioxidant diet + placebo: RHI $1.39 \pm 0.41$ vs $1.58 \pm 0.40$ ( $P > 0.05$ ) (baseline vs after 6 months). Controls: RHI $1.58 \pm 0.64$ vs $1.54 \pm 0.42$ ( $P > 0.05$ ).	Positive association between ED parameters and alpha-lipoic acid administration.
Effect of metformin on endothelial function in overweight adolescents with type 1 diabetes (T1D). Nadeau et al(20)	2016	Conference abstract	Total n=70 overweight T1D patients. n= 41 on metformin (up to 2000 mg/day), 12-19 years (mean 15.8)	n=29 placebo group. Endo-PAT scores at baseline and 13 weeks	Mean baseline RHI score was $1.8 \pm 0.6$ in the metformin group and $1.7 \pm 0.6$ placebo group. At 13 weeks, no significant change from baseline RHI ( $+0.1$ in metformin vs. $-0.0$ in placebo, $P = 0.08$ ). There was some improvement in endothelial function among males.	Metformin may improve endothelial function in overweight T1D males.
Assessment of biomarkers of inflammation and premature atherosclerosis in adolescents with type-1 diabetes mellitus. Babar et al (21)	2019	Cross-sectional study	T1D adolescents $\geq 12$ years. Two groups based on different HbA1c ranges. (HbA1c) $\leq 8.5\%$ (n=27)	HbA1c $\geq 9.5\%$ (n=25)	PAT results were not significantly different between the groups. Pearson correlation showed a significant direct relationship between rising HbA1c and PAT ( $p=0.03$ , $r=0.31$ ).	Suboptimal glycemic control as evidenced by a rising HbA1c causes early atherosclerosis.
Improvements in peripheral vascular function with vitamin D treatment in deficient adolescents with type 1 diabetes. Deda et al (22)	2018	Research article – snow balling	n=21 T1D patients followed for ~2 years. 25-OH-Vit. D levels $< 37.5$ nmol/L. Age $15.7 \pm 1.4$ years, [F/M 19/12]	Controls: matched age, sex and T1D tested spring and in fall (no significant difference noted).	After $4.8 \pm 1.3$ months of Vit. D supplementation RHI improved: $1.83 \pm 0.42$ vs $2.02 \pm 0.68$ ( $P < 0.05$ ).	Vit. D supplementation associated with improvement to endothelial function and reduced expression of urinary inflammatory markers.

166 Table 1: Endo-PAT 2000 in paediatric type 1 diabetes mellitus (T1D) patients (5 studies). Reactive hyperemia

167 index (RHI), type 1 diabetes mellitus (T1D), augmentation index (AIx) (vascular stiffness), endothelial

168 dysfunction (ED), Oxygen radical absorbance capacity units (ORAC).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Nocturnal blood pressure dipping as a marker of endothelial and cardiac function in pediatric-onset systemic lupus erythematosus (SLE). Chang et al (23)	2020	Cross-sectional study – author contacted for separate paed data	n=20, 9-19 years (mean 16.5), (7 were age 16 or under). Average disease duration 3.2 years ( $\pm$ 2.1). [F/M 17/3]	Separated into 2 groups based on nocturnal BP dipping status.	Mean ln(RHI) for n=7 (aged 16 and under): 0.529. 22% had ED. Reduced diastolic BP dipping was associated with poorer endothelial function ( $r$ 0.5, $p$ = 0.04).	SLE cohort, isolated nocturnal BP non-dipping is prevalent and associated with ED and atherosclerotic changes. Potential role for routine ABPM for youth with SLE.
Endothelial Function and Arterial Stiffness Relate to Functional Outcomes in Adolescent and Young Adult Fontan Survivors. Goldstein et al (24)	2016	Cross-sectional prospective observational study	n=60, 8-25 years (mean 13.9 $\pm$ 4.1), [F/M 29/31]	No controls	AI ( $P$ <0.05) was negatively associated with peak VO <sub>2</sub> (O <sub>2</sub> consumption). PAT derived baseline pulse amplitude ( $P$ <0.05) was negatively associated with the ratio of minute ventilation to CO <sub>2</sub> at anaerobic threshold. PAT-AI ( $P$ <0.05) was negatively associated with parent-reported Paeds QOL total and physical health summary scores.	Worse vascular measures were associated with worse functional measures. Increased arterial stiffness and decreased endothelial function are associated with lower aerobic capacity, physical activity, and quality of life in Fontan survivors.
Natural history of vascular function in adolescent and young adult Fontan survivors: A longitudinal assessment of endothelial function and arterial stiffness. Goldstein et al (25)	2017	Prospective single-centre longitudinal study, conference abstract	n=50, mean 13.7 $\pm$ 4.2 years, [F/M 23/27]	Paired testing at a mean interval of 2.0 $\pm$ 0.2 years of Fontan survivors.	Decreases in RHI (0.002 $\pm$ 0.01/yr) were not significant. AIx improved by 0.74 $\pm$ 0.3/yr ( $p$ =0.02). Changes RHI and AI did not correlate with change in peak VO (peak O <sub>2</sub> consumption). Change in BMI was a predictor for RHI (R 0.17, $p$ =0.007). Change in resting O <sub>2</sub> saturation was the only predictor of the rate of change in AI (R 0.09, $p$ =0.04).	Vascular function does not change uniformly in Fontan survivors. Changes in vascular function do not relate to changes in aerobic capacity but are associated with changes in anthropometric measures and O <sub>2</sub> saturation.
Vascular function long term after Kawasaki disease: another piece of the puzzle? Pinto et al (26)	2017	Single-centre prospective study	n=43 Kawasaki patients, age >11 years, diagnosed >5 years ago, with no coronary lesions or any other risk factors for cardiovascular disease.	n= 43 control group of individuals without cardiovascular risk factors.	Kawasaki patients had decreased RHI compared with controls (1.59 $\pm$ 0.45 versus 1.98 $\pm$ 0.41; $p$ <0.001). AI was similar in both groups (-4.5 $\pm$ 7 versus -5 $\pm$ 9%; $p$ 0.6).	Children with Kawasaki disease may have long-term sequelae, even when there is no discernible coronary artery involvement in the acute stage of the disease.
Endothelial function in	2017	Observational	n=19 with HSP, 13.5 $\pm$ 3.9 years,	n=23 healthy children, 12.8 $\pm$	Mean RHI 1.81 in the study group and 1.87 in	This study suggests that HSP causes short

children with a history of Henoch Schonlein purpura (HSP). Butbul Aviel et al (27)		prospective study	[F/M 8/11]	4.5 years, [F/M 7/16]	the control group (p = 0.18). RHI was higher in patients who had endothelial function measured >6 years since HSP diagnosis compared with those patients with less than 6 years follow up (1.98 ± 0.74 vs. 1.38 ± 0.43 P = 0.037).	term endothelial dysfunction that improves with time.
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170 Table 2: Endo-PAT 2000 in paediatric patients with cardiac and vascular conditions (5 studies). Reactive

171 hyperemia index (RHI), augmentation index (AI), systemic lupus erythematosus (SLE), ambulatory blood

Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Vascular function in asthmatic children and adolescents. Augusto et al (28)	2017	Cross-sectional controlled study	n=19 asthmatic patients, age 13.6 ± 0.6 years. [F/M 0/19]	n=18 controls. 14.9 ± 0.7 years. [F/M 0/18]	LnRHI were similar between groups (p = 0.23). The augmentation index (AIx@75%) was significantly higher in the asthmatic group (-7.75 ± 1.7) compared to the control group (-15.25 ± 1.8), p < 0.04.	The increased AIx@75 without changes in LnRHI in asthmatic patients could mean that an early detection of vascular impairment may precede ED.
The effect of weight loss on endothelial function and sleep disordered breathing (SDB) in obese children. Ysebaert et al(29)	2018	Conference abstract	n=62 obese, age 11-19 (mean 15.8) years, [F/M 20/42]	No controls. Children reassessed after 6-month weight loss programme.	Endo-Pat used. At baseline 39% had SDB. After 6 months, 86% had resolution of earlier diagnosed SDB. All showed significant improvement of endothelial function after programme (p < 0.001). No correlations between presence of SDB and improvement in endothelial function found.	Endothelial function significantly improves after weight loss.
Polysomnographic correlates of endothelial function in children with obstructive sleep apnoea (OSA). Zhang et al (30)	2018	Cross sectional study	n=121 mild OSA, 6.2 ± 1.6 years, [F/M 37/84]. n=127 moderate-severe OSA, 6.0 ± 1.6 years, [F/M 31/96]	n=107 primary snorers (PS), age 6.4 ± 1.8 years, [F/M 37/70]	OSA groups lower RHI than PS (P < 0.001, P = 0.001). RHI positively correlated with age (r = 0.17, P = 0.002), BMI z score (r = 0.14, P = 0.008) and oxygen saturation (r = 0.15, P = 0.006).	Children with OSA are at increased risk for abnormal endothelial function than habitually snoring children.
Endothelial	2020	Cross	n=248 OSAS, age	n=107 primary	OSAS had lower RHI	OSAS have

172 pressure monitoring (ABPM), Henoch Schonlein purpura (HSP).

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dysfunction in children with obstructive sleep apnoea syndrome (OSAS). Xu et al(31)		sectional study	3-11 years	snorers (PS). No significant differences in age/gender.	1.1±0.1 vrs 1.2±0.2 (P<0.01). RHI independently correlated with age, gender, obstructive apnoea hypopnea index, oxygen desaturation index (P<0.01).	significant ED compared with PS. Frequent arousals due to obstructive respiratory events during sleep may be a candidate risk factor for ED.
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174 Table 3: Endo-PAT 2000 in paediatric patients with respiratory conditions (4 studies). Natural logarithm of RHI  
 175 (LnRHI), endothelial dysfunction (ED), reactive hyperaemia index (RHI), augmentation index (AI), heart rate-  
 176 corrected augmentation index (AIx@75), primary snorers (PS), obstructive sleep apnoea (OSA), obstructive  
 177 sleep apnoea syndrome (OSAS).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Do self-reported stress and depressive symptoms effect endothelial function in healthy youth? The LOOK longitudinal study. Olive et al(32)	2018	Longitudinal cohort study	n=203, 7.6 ± 0.3 years, [F/M 111/92].	LOOK longitudinal study, who were followed through to adolescence (16 years).	All relationships occurred in the hypothesised direction, but no cross-sectional or prospective evidence of early psychological stress or depression was associated with ED (all p > 0.05).	Contrast to previous findings in adolescents, little evidence between current or previous psychosocial stress or depression and endothelial function in 16-year-old adolescents.

182



Cerebrovascular reactivity is associated with peripheral endothelial function (EF) among adolescents. Urback et al(33)	2016	Conference abstract	n=11 with bipolar disorder. EF measured by PAT and cerebrovascular reactivity (CVR) by blood-oxygen-level dependent fMRI.	n=35 healthy controls	EF was positively correlated with CVR in grey matter ( $r=0.41$ , $p=0.012$ ), and a peak voxel in the left-medial-frontal gyrus ( $r=0.35$ , $p=0.036$ ).	Breath-hold CVR and peripheral EF are linked, suggesting that vascular function may be a multi-systemic phenotype. EF may be a potential proxy for cerebral blood vessel function with greater accessibility and lower cost than fMRI.
Retinal-vascular photography as a window into the cardiovascular and neurocognitive burden of adolescent bipolar disorder (BD). Naiberg et al (34)	2017	Cross-sectional study, author emailed for separate paediatric data-most were teenagers	n=30 with bipolar disorder, 17.97±1.86 years	n=32 healthy controls, 16.00±1.62 years	In BD group, higher endothelial function associated with higher arterio-venular ratio ( $r=0.375$ , $p=0.041$ ).	Retinal photography may help assessing cardiovascular and neurocognitive burden of BD.
Impact of psychological health on peripheral endothelial function and the HPA-axis activity in healthy adolescents. Chen et al(35)	2017	Longitudinal 3-year follow-up study	n=162, 14.5 ± 1 years. [F/M 94/68].	Baseline and three-year follow-up.	Lower peripheral endothelial function was associated with high level of anger ( $\beta = -0.332$ , $p = 0.018$ ) and disruptive behaviour ( $\beta = -0.390$ , $p = 0.006$ ) over three years in males, but not in females, adjusted for covariates.	High amounts of negative emotions may have adverse effects on peripheral endothelial function and regulation of the HPA-axis activity. High level of self-concept might be protective.

183 Table 4: Endo-PAT 2000 in paediatric patients with psychiatric conditions (4 studies). Endothelial dysfunction  
 184 (ED), endothelial function (EF), cerebrovascular reactivity (CVR), bipolar disorder (BD), functional magnetic  
 185 resonance imaging (fMRI), hypothalamic–pituitary–adrenal HPA.

186

Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
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1 2 3 4 5 6 7 8 9 10	Vascular endothelial function in inflammatory bowel disease (IBD). Winderman et al(36)	2018	Case-control study	n=16 with IBD (all in clinical remission), age 16.7 +/- 2.6 years, [F/M 8/7]	n=16, age 15.1 +/- 2.8 years, [F/M 7/8]	RHI IBD vs controls 1.66 vs 2.02 (P =0.036). IBD group had a mean RHI within the range associated with VD risk in adults (1.67).	IBD group lower RHI compared with controls. IBD patients may need to be monitored for thromboembolic phenomena.
11 12 13 14 15 16 17 18 19	Endothelial health in childhood acute lymphoid leukaemia (ALL) survivors: pilot evaluation with peripheral artery tonometry. Ruble et al (37)	2015	Case control study	n=16 ALL survivors, age 8-20 years (12.9+/- 0.9), [F/M 8/8].	n=16 healthy sibling pairs 13.8 (0.9), [F/M 10/6].	Both groups similar in cardiovascular risk measures but survivors had lower RHI (1.54 vs. sibling 1.77; P=0.0474).	Evidence of poorer vascular health in cancer survivors.
20 21 22 23 24 25 26 27 28 29 30	Microvascular endothelial function in Japanese early adolescents. Odanaka et al (38)	2017	Control study	n=157 healthy adolescents divided by gender. Females n=82, median age 14 (1), 13.7 ± 0.9 years	Males n= 75, median age 14 (2) years	No difference in RHI according to sex: boys and girls 1.85 ±0.6, 1.82 ±0.66 and 1.87± 0.54. RHI was significantly associated with systolic and diastolic BP, and had no correlation with anthropometric parameters and arterial stiffness markers.	RHI among adolescents were similar to those reported in previous studies on children and early adolescents.
31 32 33 34 35 36 37 38 39 40 41	Endothelial Dysfunction and the Effect of Arginine and Citrulline Supplementation in Children and Adolescents With Mitochondrial Diseases. Al Jasmi, et al (39)	2020	Case control study	9 participants, age 6-17 years (mean 9.6).	3-15 years (mean 9.4). Baseline endothelial dysfunction was assessed in control individuals.	Lower RHI with mitochondrial diseases. RHI increased with arginine or citrulline supplementation	Supplementation with NO precursors may improve ED by enhancing NO production. First study to use Endo-PAT methodology in mitochondrial diseases.
42 43 44 45 46 47 48 49 50 51 52 53 54	Assessment of traditional and non-traditional risk factors for premature atherosclerosis in children with juvenile dermatomyositis (JDM) and pediatric controls. Wahezi et al (40)	2020	Retrospective controlled study	n=40 JDM, age 6-22 (mean 12.4± 4.1) years, [F/M 28/12]	n=20 controls, age 12.7± 3.9 years, [F/M 14/8]	75% controls had ED compared to 50% JDM group. RHI controls and JDM groups: 1.43 [1.2, 1.7] and 1.57 [1.2,1.9]. When controlled for lipoprotein A (atherogenic confounder), JDM patients had 41% RHI increase, thus indicating less ED compared to controls.	Rheumatology childhood disorders may be at increased risk of developing premature atherosclerosis, but traditional and sociodemographic features may play a greater role in the ultimate development of cardiovascular disease.
55 56 57 58 59 60	Vascular Health of Children Conceived via In Vitro Fertilization (IVF). Zhang et al	2019	Cross-sectional pilot study	n=17 IVF children, 10-14 years. Also used carotid ultrasound and pulse wave velocity	Compared to published norms or to historical Stanford controls	Mean Endo-PAT index in the IVF cohort was 1.66+/-0.52, 71% had abnormal values (<1.9). Mean RHI was not significantly	Children conceived by IVF seem to have evidence of abnormal vascular health.



(41)			measurements.		different between IVF and controls.	
Endothelial dysfunction in South African youth living with perinatally acquired human immunodeficiency virus (PHIV) on antiretroviral therapy. Mahtab et al (42)	2020	Case control study	n= 431 PHIV, median 14.1 (12.8, 15.5) years, [F/M 213/218]	n=93 without HIV, median 13.9 (12.1, 15.3) years, [F/M 53/40]	PHIV had higher rates of ED (50% vs 34%; P = .01); relationship persisted after adjusting for age, sex, BMIZ, elevated BP, and hypercholesterolemia (RR, 1.43; P=0.02). PHIV, CD4 count, viral load and current ART class were not associated with ED after adjustment.	PHIV appear to have increased risk of ED. These findings have important implications as HIV has increased risk of premature CVD and complications.
Soluble CD14 (sCD14) is associated with endothelial dysfunction in South African youth on ART. Dirajlal-Fargo et al (43)	2020	Case control study	n=283 perinatally acquired HIV (PHIV), 9-14 years.	n=69 age-matched without HIV	PHIVs had lower RHI despite viral suppression (RHI=1.36 vs 1.52, p<0.01). sCD14 at 24 months correlated with ED (p<0.04). PHIV with ED, sCD14 was associated with lower RHI ( $\beta$ -0.05, p=0.01).	Higher sCD14 is independently associated with ED in PHIVs.

188 Table 5: Endo-PAT 2000 in paediatric patients with other miscellaneous paediatric conditions (8 studies).

189 Reactive hyperemia index (RHI), augmentation index (AIx) (vascular stiffness), endothelial dysfunction (ED),  
 190 inflammatory bowel disease (IBD), acute lymphoid leukaemia (ALL), nitric oxide (NO), perinatally acquired  
 191 human immunodeficiency virus (PHIV), In Vitro Fertilization (IVF), soluble CD 14 (sCD14).

192

193 Many of the papers did not include other factors that would be important in a cardiovascular

194 assessment of children, for example family history, cholesterol and blood pressure parameters and

195 Body Mass Index (BMI) and standardised BMI (SDS) measurements. So, in many studies it cannot be

196 excluded that there were confounding variables affecting the ED score. Regardless, this study

197 indicates that there are a significant number of published paediatric papers that indicate the presence

198 of ED in children as young as 8 years old.

199 Several factors may impact microvascular function. For example, puberty, which is of particular

200 interest in our paediatric review. Bhangoo et al report improved RHI in correlation with an increase in

201 Tanner stages and postulated that this may be due to sex steroids(44).

1  
2  
3 202 Strengths of the paper include a comprehensive literature search including contacting authors by email  
4  
5 203 for separate paediatric results in studies with combined adult and paediatric data. All study types were  
6  
7 204 reviewed and even the studies without results but had interesting points were included in our  
8  
9 205 discussion. Also, we do not think that this paediatric Endo-PAT review has been done before.

11  
12 206 Weaknesses of the paper include there may be significant findings in studies in the grey literature or  
13  
14 207 in conference presentations that was not included, for example in the studies where 25 authors did not  
15  
16 208 respond to emails. Only papers from 2015 to date were included.

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### 20 21 22 210 **Endothelial dysfunction in paediatric type 1 diabetes mellitus patients:**

23  
24  
25 211 *Table 1* presents 5 studies in T1D patients. 3/5 studies reported RHI changes in the T1D group. 1/5  
26  
27 212 studies included only adolescent and reported that RHI negatively correlates with impaired metabolic  
28  
29 213 control and subclinical signs of autonomic neuropathy. However, regular physical activity is  
30  
31 214 protective(18). Suggesting that good metabolic control ( $HbA1c \leq 7.5\%$ ) and regular physical activity  
32  
33 215 might be protective against ED.

34  
35  
36 216 1/5 studies report the positive association between ED parameters and alpha-lipoic acid administration  
37  
38 217 and antioxidant diet(19). 1/5 reported RHI values after metformin use and this may improve  
39  
40 218 endothelial function in overweight T1D males(20).

41  
42  
43 219 Barber et al report suboptimal glycaemic control as evidenced by a rising HbA1c causes early  
44  
45 220 atherosclerosis(21). 1/5 studies noted an improvement in RHI post vitamin D supplementation in T1D  
46  
47 221 patients with vitamin D deficiency(22).

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### 51 52 53 223 **Endothelial dysfunction and Metabolic Syndrome:**

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56 224 24 studies (*Supplementary Table 1*) describe the use of Endo-PAT 2000 for metabolic syndrome.

57  
58 225 These studies included measurement of the following parameters: BMI, T1D, T2D, gender, pubertal  
59  
60 226 stage, age, polycystic ovary syndrome, blood pressure values, non-alcoholic fatty liver disease,

227 obstructive sleep apnoea, lipid profile, insulin, plasma glucose levels, inflammatory markers (urinary  
228 markers, CNP, micro-RNA-126, E-Selectin).

229 19 studies focused on obesity/overweight paediatric patients. In numerous studies, RHI was  
230 significantly lower in the obese group(45-50). ED may mediate the link between obesity-related  
231 insulin resistance and early microalbuminuria(51). Exercise and diet control improves glycolipid  
232 metabolism. Noma et al (2017) report the beneficial effects of exercise in paediatric patients and is an  
233 important message in reducing future endothelial complications(52).

234 6 studies focused on patients with impaired glucose tolerance or T2D. Studies also compared RHI in  
235 T1D and T2D patients. Kochummen *et al* (2019) mean RHI in obese adolescents without diabetes was  
236 similar to T1D and T2D patients(45). Tomsa et al (2016) RHI was higher if HbA1c was less than  
237 5.5%, and was lower in T2D obese(53).

238 Lower insulin sensitivity in these patients poses a risk of diabetic nephropathy(6). Microangiopathic  
239 renal damage increases oxygen consumption and increases resistance in the afferent arterioles. Shah et  
240 al (2017) report T2D patients have greater vascular thickness and stiffness and worse endothelial  
241 function compared to obese and lean children(54). This is raising concern that adolescents with T2D  
242 are already at risk of developing early onset cardiovascular disease.

243 Berardinelli-Seip syndrome is a rare condition characterized by severe insulin resistance and absence  
244 of subcutaneous fat since birth or early childhood. Lipids can deposit in muscle, liver and arterial  
245 walls; explaining its clinical complications of diabetes, hepatic injury, hyperlipidaemia and premature  
246 atherosclerosis. Fernandes et al (2015) used Endo-PAT 2000 in a cohort with this syndrome(55). 50%  
247 had ED (natural logarithm RHI index of  $0.49 \pm 0.15$ ). Their results support the risk of ED in this cohort  
248 and highlights the necessity of early intervention to avoid cardiovascular complications.

#### 249 **Endothelial dysfunction in cardiac and vascular conditions:**

250 Dietz et al (2015) systematic review and metaanalysis on peripheral ED in Kawasaki disease, report  
251 that patients with coronary arterial aneurysms had higher surrogate markers for cardiovascular disease  
252 risk(56). This may indicate these patients should be monitored for CVD in adulthood, however

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3 253 significant heterogeneity was reported. Two studies include ED in patients with systemic lupus  
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5 254 erythematosus (SLE) and Henoch Schonlein purpura (HSP).  
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7  
8 255 Goldstein et al (2016) by using Endo-PAT identified multiple patient and procedural factors for  
9  
10 256 Fontan survivors(57). Some determinants of RHI included prior Norwood procedure, systolic blood  
11  
12 257 pressure, resting heart rate and oxygen saturation. Targeted intervention of modifiable risk factors  
13  
14 258 may improve long-term vascular health and functional status in Fontan survivors. Further research by  
15  
16 259 Goldstein et al (2015) noted increased arterial stiffness and decreased endothelial function are  
17  
18 260 associated with lower aerobic capacity, quality of life (QOL) and physical activity in adolescent and  
19  
20 261 young adult Fontan survivors(58).  
21  
22  
23 262 ‘The LOVE-COARCT study’ (Long-term Outcomes and Vascular Evaluation After Successful  
24  
25 263 Coarctation of the Aorta Treatment) compares vascular function in patients with coarctation of the  
26  
27 264 aorta treated with surgery, balloon dilation or stenting. Endothelial function was similar among  
28  
29 265 groups(59).  
30  
31  
32 266 Negishi et al (2016) used Endo-PAT to compare Fontan survivors and healthy controls. The Fontan  
33  
34 267 patients were aged 15 to 32 years. Mean RHI 0.56+/- 0.26 in Fontan patients and 0.78+/- 0.31 in  
35  
36 268 controls (p= 0.09). RHI in Fontan patients was associated with diastolic blood pressure, heart rate and  
37  
38 269 haemoglobin A1c level(60). Endothelial function in Fontan patients was associated with abnormal  
39  
40 270 glucose tolerance and arterial stiffness and therefore concluded that glucose regulation might be a  
41  
42 271 potential target to improve ED in this cohort.  
43  
44  
45 272 Adult patients with repaired coarctation of aorta have a high risk of late HTN. Nozaki et al (2018)  
46  
47 273 assessed ED in conduit and resistance arteries and used FMD and Endo-PAT in paediatric patients  
48  
49 274 with repaired coarctation of aorta(61).  
50  
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52  
53 275 **Endothelial dysfunction in respiratory conditions:**  
54  
55  
56 276 Augusto et al noted an increased augmentation index without changes in LnRHI in asthmatic patients;  
57  
58 277 indicating early detection of vascular impairment may precede ED, and different mechanisms may  
59  
60 278 contribute to the pathogenesis and progression of cardiovascular events in this population(28).

1  
2  
3 279 1/4 reported an improvement in sleep disordered breathing post weight loss(29). Also, endothelial  
4  
5 280 function significantly improves after weight loss. 2/4 studies report children with OSA compared to  
6  
7 281 habitual snorers are at increased risk for ED(30, 31). Frequent wakening due to obstructive respiratory  
8  
9 282 events may be a risk factor for ED in OSA.

### 283 **Endothelial dysfunction and psychological conditions:**

14  
15 284 Potential limitations in this area are self-reported methods for detecting psychological distress of  
16  
17 285 children, for example in the LOOK longitudinal study(32). Naiberg et al (2017) utilised retinal  
18  
19 286 vascular photography, a proxy for cerebral microvasculature, and Endo-PAT to assess cardiovascular  
20  
21 287 and neurocognitive burden in bipolar disorder (BD) adolescents (mean age 16-17 years)(34). In the  
22  
23 288 BD group, better endothelial function was associated with higher arterio-venular ratio ( $r=0.375$ ,  
24  
25 289  $p=0.041$ ). Retinal vascular calibre was significantly associated with endothelial function in BD and it  
26  
27 290 has been suggested that it may be used as an assessment tool in this cohort.

29  
30 291 Olive L.S. (2017) published 'The emerging field of paediatric psycho-cardiology' highlighting the  
31  
32 292 importance of the childhood origins of adult CVD(62). This article highlights that psychological  
33  
34 293 distress can influence CVD risk, directly by physiological change that can negatively impact the  
35  
36 294 integrity of the cardiovascular system.

### 39 295 **Conclusion:**

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42 296 There are a number of papers in the paediatric literature describing ED at young ages using Endo-  
43  
44 297 PAT. It should be concerning to paediatricians that children with various chronic diseases have  
45  
46 298 evidence of ED. However, in many cases, there has only been a single cohort study using Endo-PAT.  
47  
48 299 Further studies are required to validate these findings. Additionally, longitudinal studies are required  
49  
50 300 to evaluate how this ED may change as the child ages and their chronic conditions changes. Further  
51  
52 301 studies are also required that will characterise more completely the cardiovascular risk profile of these  
53  
54 302 children with chronic disease. Consensus on other vascular risk markers that could be included in  
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56 303 future studies is ideal and if accomplished, this would facilitate meta-analyses of studies of conditions  
57  
58 304 with relatively rare conditions. Paediatricians should start to include an approach to cardiovascular  
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3 305 risk assessments in their assessments of young children and adolescents, including but not limited to  
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5 306 those with chronic diseases.  
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16 310 **Statements and declarations:**

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19 311 **a. Authorship contributions:**

20  
21  
22 312 All authors contributed to the initial search strategy protocol. I deLaunois performed the online  
23  
24 313 database search. J Hayden and G McDonnell separately performed a blind screen of the abstracts and  
25  
26 314 analysed the papers. G McDonnell contacted the authors of joint adult and paediatric papers to obtain  
27  
28 315 separate paediatric data. J Hayden wrote the initial manuscript which was revised by C O’Gorman.  
29

30 316 All authors reviewed the manuscript prior to submission.  
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32

33 317 **b.** There are no competing interests to declare.  
34  
35

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37  
38 319 commercial or not-for-profit sectors.  
39  
40

41 320 **d.** Data sharing: search technique and data analysis are available from Rayyan software and the  
42  
43 321 corresponding author.  
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46 322 **e.** Competing Interest: None declared  
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49 323  
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51 324 **References:**

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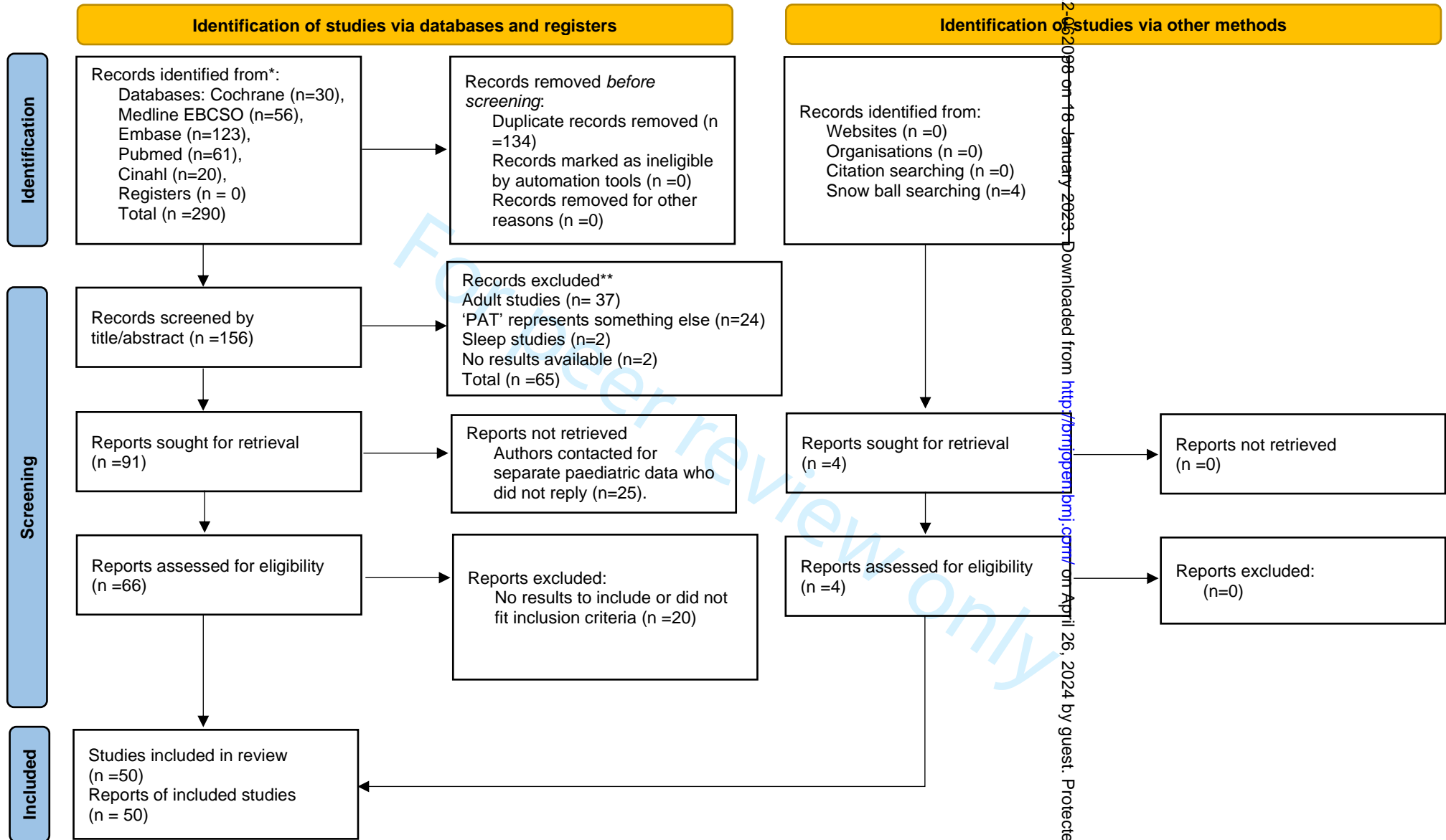
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25 497 Figure 1: PRISMA 2020 Flow diagram of systematic search for Endo-PAT 2000 in paediatric  
26 498 populations.

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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

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## Supplemental material:

### Endothelial dysfunction and other paediatric conditions

#### *Childhood cancer survivors:*

Chemotherapy causes cardiomyocyte damage and also negatively affects endothelial function.

Broberg et al (2018) utilised Endo-PAT 2000 in childhood cancer survivors and noted a lower RHI in this cohort compared to controls(1). Brouwer et al (2013) studied cancer survivor patients after potential cardiovascular toxic treatment (e.g. anthracyclines, platinum) and/or radiotherapy and noted a higher risk of ED compared with sibling controls(2). Broberg et al (2016) identified one-third of cancer survivors (31.2%) compared to 8% of controls ( $p=0.02$ ) had ED in their study(3). They concluded this may be a useful screening tool of cardiovascular disease in asymptomatic cancer survivor patients.

Pao et al (2018) assessed the relationship between blood pressure and ED using Endo-PAT 2000 in haematopoietic stem cell transplant recipients. Hypertension on ambulatory blood pressure monitoring ( $p=0.045$ ) and blunted nocturnal dipping ( $p=0.04$ ) were associated with a lower Endo-PAT scores(4).

Jehlicka et al (2011) used Endo-PAT and noted ALL patients had lower RHI compared to controls ( $1.57\pm0.50$ ,  $1.96\pm0.63$ ;  $p\leq0.05$ )(5).

#### *Autoimmune conditions:*

Children with autoimmune diseases may have a high tendency to develop ED which was highlighted in a study using a novel technique(6). Atherosclerosis is an emerging cause of morbidity and mortality in patients with rheumatological conditions such as juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), dermatomyositis, etc. Borenstein-Levin et al assessed a cohort with autoimmune conditions compared to controls and 29% in the study group had ED compared to 6% in the control group ( $p<0.05$ )(6).

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3 In SLE patients, ED may occur from impaired clearance of apoptotic cells, oxidative stress, B cell  
4 activation with different circulating autoantibodies, etc(7). Regular ED assessment in SLE patients  
5 has been recommended due to risk of subclinical atherosclerosis(7).  
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10 ***Metabolic diseases:***

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12 Yano et al research in Fabry disease patients demonstrated that early diagnosis of ED can help  
13 determine the timing of initiating enzyme replacement therapy(8). Utilizing RH-PAT as a screening  
14 tool for early renal involvement may be helpful as it may detect abnormalities even prior to  
15 microalbuminuria(9). This can provide guidance on enzyme replacement therapy which is required to  
16 prevent irreversible progressive renal failure.  
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19 Al Jasmi et al research in mitochondrial diseases reported that arginine or citrulline supplementation  
20 may improve ED, which provides evidence that these amino acids may be therapeutic(10).  
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29 ***Turner syndrome:***

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31 Turner syndrome (TS) patients have increased cardiovascular risk factors which predispose to cardiac  
32 and cerebrovascular complications. A literature review concluded that TS have unfavourable  
33 cardiometabolic risk factors which predispose them to adverse cardiac and cerebrovascular outcomes  
34 in young adulthood(11). It is unclear whether this is secondary to the syndrome itself or from  
35 modifiable risk factors such as obesity, hypertension, etc. Moreover, congenital heart disease is a  
36 clinical feature in 30% of cases of TS patients. There is a huge emphasis on the importance of regular  
37 screening in this cohort and also further research into whether any variables could potentially be  
38 altered to reduce the atherosclerosis risk in adulthood.  
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49 O’Gorman et al (2012) published a case-control study on TS patients(12). This paper excluded any  
50 with structural congenital heart disease. Lower RHI scores in TS compared with controls 1.64  
51 (0.34) vs 2.08 (0.32) (P<0.005). Growth hormone may protect endothelial function in TS patients  
52 as GH-untreated RHI 1.44 (0.26) versus GH-treated 1.86 (0.28) (p P<0.05).  
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58 ***Inflammatory bowel disease:***

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3 One study in our review (*Table 6*) highlights that IBD patients had lower RHI compared with  
4 controls(13). Petr et al (2014) provided evidence of increased ED in children with Crohn's disease  
5 compared to healthy controls(14). RHI values were significantly lower in the patients with Crohn's  
6 than controls ( $p < 0.05$ ).  
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### 10 11 12 ***Infectious diseases:*** 13

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15 Dirajlal-Fargo et al (2017) used Endo-PAT 2000 to assess ED in perinatally acquired HIV patients.  
16 Perinatally acquired HIV patients appear to have higher levels of ED (lower RHI 1.34 (1.20,  
17 1.42) compared with control group 1.52 (1.27, 1.80) ( $p < 0.01$ ))(15).  
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21 The pathogenesis of severe Plasmodium vivax malaria is poorly understood. ED and reduced nitric  
22 oxide (NO) bioavailability characterize severe falciparum malaria. Barber et al (2016) identified that  
23 endothelial function was impaired in proportion to disease severity. Those with severe vivax malaria,  
24 non-severe and healthy controls median RH-PAT index 1.49, 1.73, and 1.97 respectively  
25 ( $p = 0.018$ )(16). ED in this cohort was associated with reduced L-arginine bioavailability, which may  
26 contribute to microvascular pathogenesis.  
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### 34 35 ***Haematological conditions:*** 36

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38 Sivamurthy et al (2009) reported lower RHI in the majority sickle cell disease in a paediatric  
39 population (1.53 and 1.71;  $p$  value .032). RHI was not normal in children with chronic transfusions or  
40 hydroxyurea(17).  
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### 45 46 ***Very low birthweight babies:*** 47

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49 Harris et al (2020) assessed cardiovascular outcomes for those born with very low birth weights  
50 (VLBW)  $< 1500$ g. The VLBW cohort ( $n = 229$ ; 71% of survivors) and term-born controls ( $n = 100$ ),  
51 were assessed at age 26-30 years. The VLBW cohort had lower RHI compared to controls(18).  
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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Assessment of Microvascular Function in Children and Adolescents with Diabetes and Obesity. Kochummen et al(1)	2019	Cross-sectional study	DM group. n=33 T1D with normal weight. n=8 obese T2D, age 12.7 (3.8) years, [F/M 25/16]	n=17 obese, non-DM children (normal BGL, BP and lipid profile), 12.8 (2.7) years, [F/M 9/8]	For every 1% increase in HbA1C, RHI decreased by 0.097 (P = 0.01). RHI of DM group with HbA1C <10% ( $1.70 \pm 0.58$ ) versus those with $\geq 10\%$ ( $1.21 \pm 0.19$ ) (p= 0.02).	Poorly-controlled DM (HbA1C $\geq 10\%$ ) had lower RHI. RHI negatively related with HbA1C. RHI similar between obese and normal weight with T1D. Similar between T1D and T2D.
Effects of a dietary strawberry powder on parameters of vascular health in adolescent males. Djurica et al (2)	2016	Randomised, double-blind, cross-over study	n=15 overweight /obese males, 14-18 years (mean 16). 1 week of 50 g of a freeze-dried strawberry powder (FDSP) or a control powder, daily. Before and after plasma nitrate/nitrite levels measured.	10 control powder, 14-18 years (mean 16).	Acute plasma nitrate/nitrite levels increased 1 h after consuming the FDSP (P<0.001). When nitrate levels increased after FDSP intake compared to controls, had an increase in RHI (P=0.014).	Strawberries can provide vascular health benefits to heavier adolescent males.
Non-alcoholic Fatty Liver Disease in Hispanic Youth with Dysglycemia: Risk for Subclinical Atherosclerosis? Bacha et al (3)	2017	Cross-sectional study	n=23 overweight/ obese with NAFLD, age $15.3 \pm 0.4$ years. n=20 prediabetes, n=16 T2D, [F/M 12/11]	n=13 overweight/ obese without NAFLD, age $15.3 \pm 0.4$ years, with pre-diabetes or T2D, [F/M 3/10]	NAFLD group had lower RHI ( $1.4 \pm 0.05$ vs $1.7 \pm 0.09$ , p= 0.002), greater AIx ( $-6.0 \pm 1.6$ vs $-12.0 \pm 2.1$ , P = 0.03). Hepatic fat inversely related to RHI (r = -0.49, P = 0.002) and positively related to AIx (r = 0.45, P = 0.006).	Hepatic fat and AST/ALT levels were inversely related with RHI. If dysglycemia, NAFLD is associated with worse endothelial function.
Circulating fibroblast growth factor-21 (FGF-21): A biomarker of subclinical atherosclerosis in obese youth with non-alcoholic fatty liver disease (NAFLD)? Bacha et al (4)	2017	Conference abstract	Obese adolescents with NAFLD, $15.4 \pm 0.3$ years. n=13 normal glucose tolerance, n=19 prediabetes, n=16 T2D patients	Control group: no NAFLD. No difference in age/gender between groups.	Lower RHI in NAFLD group and higher AIx-75. FGF-21 concentrations were related to RHI (r=-0.33, p=0.03) and AIx (r=0.45, p=0.02).	Circulating FGF-21 levels are elevated in obese youth with NAFLD and are associated with measures of insulin sensitivity and ED. FGF-21 may constitute a biomarker of higher risk for vascular dysfunction in these youth.
Flow-mediated dilation in obese adolescents: Correlation with waist circumference (WC) and systolic blood pressure	2018	Case control study	n=20 obese patients, median age 14 years	n=10 normal weight, median age 15 years, paired for gender	No difference in RHI between groups. 35% obese group had metabolic syndrome, none in control group. OSA in 86.6% obese and 50% of normal weight group.	Obese group had evidence of ED and metabolic syndrome. Increased WC and SBP seem to be involved in this finding.



(SBP). Hussid et al (5)						
Improvement of microvascular endothelial dysfunction induced by exercise and diet is associated with microRNA-126 in obese adolescents. Donghui et al (6)	2019	Quasi-randomized study	n=57 obese male adolescents, 12-18 (15.38 ± 2.82) years, [F/M = 0/57], 6-week exercise program with dietary intervention.	n=10 normal weight adolescents, 15.38 ± 2.82 years, maintained sedentary. Age 12-20, n = 10 [F/M 0/10]	Obese group 1.43 (0.35) vs controls 1.67 (0.36) (p< 0.05). After 6 weeks intervention RHI increased (p <0.01), while microRNA-126 significantly decreased (p<0.01). miRNA-126 positively correlated with ΔRHI (r = 0.69, p<0.05).	RHI higher in controls. RHI improved in obese group after exercise and diet interventions. Findings might be related to changes in serum miRNA-126.
Distribution of peripheral arterial stiffness and endothelial function as well as their correlations with cardiovascular risk factors in children and adolescents. Mu et al (7)	2016	Cross-sectional population-based study, conference abstract	n=94 obese, 7-17 years, used automatic waveform analyser (BP-203RPE-I) and Endo-PAT 2000.	n=452 normal-weight	In normal weight group, RHI increased with age (r=0.33, P<0.01; r=0.36, P<0.01). RHI positively correlated with BMI (r=0.10, P=0.018) but negatively correlated with DBP (r=-0.10, P=0.016). RHI did not differ between genders.	Brachial-ankle pulse wave velocity (baPWV) and RHI increased along with age; arterial stiffness and endothelial function continued to develop in the normal weight group.
Urine Albumin-to-Creatinine Ratio (UACR): A Marker of Early Endothelial Dysfunction in Youth. Bartz et al(8)	2015	Control study	15.6 ± 0.2 years, n=25 overweight with normal glucose tolerance, [F/M 17/8]. n=20 overweight with prediabetes, [F/M 11/9].	n=13 normal weight, 16.3 ± 0.4, [F/M 7/6].	Fasting UACR was analysed. Normal weight group had higher RHI (1.84 ± 0.1, 1.56 ± 0.1, and 1.56 ± 0.1, P = .04). UACR was related to RHI (r = -0.33, p = .01).	UACR is an early marker of endothelial dysfunction in youth, independent of glycemia.
Urinary biomarkers as indicator of chronic inflammation and endothelial dysfunction in obese adolescents. Singh et al(9)	2017	Research article, control study	n=63 total. n=14 overweight (OW), n=29 obese, age 13.8 (2.4), [F/M 23/20]	n=20 normal weight (NW), age 13.9 (2), [F/M 8/12]	There were no differences in RHI levels among the study groups. NW 1.6 (0.1), OW 1.66 (0.1) and obese 1.67(0.1). NW girls RHI 1.9 vs NW boys 1.25.	No significant correlation between RHI and urinary markers. RHI higher in NW female adolescents.
Prevalence of Type D personality in obese adolescents and associated cardiovascular risk. Bruyndonckx et al(10)	2018	Control study, conference abstract	Obese adolescents-no definite numbers (conference abstract only)	Healthy normal weight children	Positive correlation in obese adolescents between negative affectivity and vascular stiffness (r= 0.28; p= .04)	Obese adolescents have worse cardiovascular risk profile with ED.
Endothelial function and arterial stiffness in obese adolescents - A relation to baroreflex function.	2017	Conference abstract	n=22 obese, 15.28 +/- 2.8 years, [F/M 10/12]	n=22 non-obese, 15.98 +/- 2.46 years, [F/M 10/12]	No significant difference in RHI (p = 0.473). Baro-reflex sensitivity was also calculated.	No difference in RHI between groups. Findings require further study.

Czippelova et al(11)						
Obesity in children and adolescents: A relation to endothelial function and arterial stiffness. Czippelova et al(12)	2016	Conference abstract	n=16 obese adolescents, 15.22 +/- 2.2 years, [F/M 7/9]	n=16 non-obese, 16.22 +/- 1.5 years, [F/M 7/9]	Significant difference in RHI (p = 0.018) with RHI higher in obese group (1.66 +/- 0.28 vrs 1.4 +/- 0.25).	Less early atherosclerotic changes in obese group which was in contrast to expectations: requires further study.
Endothelial function in youth: A Biomarker modulated by adiposity-related insulin resistance. Tomsa et al (13)	2016	Cross sectional study	Total n = 60. n=25 obese without DM, n=19 obese with impaired glucose tolerance, n=16 obese T2D but Hb1Ac < 8%. Age 15.5 (0.2), [F/M 37/23]	n=21 normal weight, age 15.5 (0.2), [F/M 9/12]	RHI inversely related to % body fat (r = -0.29, P = .008), total (r = -0.37, P = .004), subcutaneous (r = -0.39, P = .003), and visceral abdominal fat (r = -0.26, P = .04). Aix at heart rate 75 bpm was higher (worse) in the lower RHI groups (P = .04).	Childhood obesity is associated with ED: lower RHI and higher Aix. RHI lower in obese and T2D. RHI negatively related with percentage body fat, WC, Leptin, TNF-alpha, blood glucose.
Free Vitamin D: Relationship to Insulin Sensitivity and Vascular Health in Youth. Bacha et al (14)	2019	Cross-sectional study	n=79, age 15.4 ± 0.2 years, [F/M 45/34]. n=30 overweight. n=31 overweight with prediabetes	n=18 normal weight and normal glucose tolerance. Across tertiles of free 25(OH)D concentrations	The lowest tertile group had lower RHI (1.42 ± 0.06, 1.54 ± 0.06, and 1.77 ± 0.09, P = 0.002), compared with the second and third tertiles.	Youth with low free 25(OH)D or BioD concentrations have lower insulin sensitivity and worse endothelial function.
Preclinical vascular alterations in obese adolescents detected by Laser-Doppler Flowmetry technique. Fusco et al (15)	2020	Research article	n=22 obese adolescents, 14.11 +/- 2.53, [F/M 13/9]	n=24 normal-weight, 15.2 +/- 1.56, [F/M 11/13]	Similar RHI between obese and non-obese groups (1.80 +/- 0.62 and 1.86 +/- 0.51).	RHI not different between groups. RHI did not correlate with LDF (that is impaired in obese).
Impaired endothelial function in adolescents with overweight or obesity measured by peripheral artery tonometry. Pareyn et al (16)	2015	Cross sectional study	n=27 overweight or obesity, 14.7 (13.0–16.4) years, [F/M 11/16]	n=25 normal weight controls, 15.5 (13.9–16.2) years, [F/M 13/12]	RHI normal weight 1.88 (1.7–2.4) vs OW/obese 1.5 (1.3–1.9) (P< 0.05). Lower RHI if OW/obese, and higher baseline pulse amplitude (p = 0.027 and p < 0.0001). Significant positive correlation between baseline pulse amplitude and BMI in OW/obese group. RHI positively correlated with age and tanner stage (P< 0.05). RHI negatively correlated with DBP (P< 0.05).	ED measured by lower RH-PAT score and higher baseline pulse amplitude, was present in OW group. First time in the literature to report significant difference in baseline pulse amplitude between OW adolescents compared to their peers.

1 2 3 4 5 6 7 8 9 10 11 12 13 14	C-type natriuretic peptide (CNP) plasma levels and whole blood mRNA expression show different trends in adolescents with different degree of endothelial dysfunction. Del Ry et al(17)	2020	Research article -snow balling	n=16 primary obesity, not DM, age 13.3 (0.5) years, [F/M 8/8].	n=24 normal weight, age 14.3 (0.4) years, [F/M 14/10].	RHI normal weight 2.1 (0) vs obese 1.4 (0) (P< 0.005). RHI negatively associated with CNP and diastolic BP (P< 0.005).	RHI significantly lower in obese group. RHI negatively related with CNP, DBP, fat mass and HbA1C.
15 16 17 18 19 20 21 22	C-type natriuretic peptide (CNP) is closely associated to obesity in Caucasian adolescents. Del Ry et al (17)	2016	Research article -snow balling	n=10 overweight, age 12.8 (1.6) years, [F/M 5/5]. n=45 obese, 12.8 (1.6) years, [F/M 19/26]	n=27 normal weight, age 12.8 (1.4) years, [F/M 14/13]	Normal weight group RHI 2.1 (0.2) vs OW 1.6 (0.4) (P< 0.05). Normal weight vs obese group RHI 1.4 (0.3) (P< 0.005). RHI negatively associated with CNP (P< 0.005).	RHI significantly lower in overweight/obese groups. CNP negatively related with RHI.
23 24 25 26 27 28 29 30 31	Arterial Stiffness and Endothelial Function in Young Obese Patients - Vascular Resistance Matters. Czippelova et al (18)	2019	Research article	Author contacted for separate paed data. n=16 obese group, age <16 years, [F/M 7/9]	n=15 controls, age <16 years, [F/M 7/8]	RHI control vrs obese groups: 1.320 ± 0.427 and 1.457 ± 0.280. RHI obese girls and boys: 1.410 ± 0.253 and 1.494 ± 0.308. RHI control girls and boys: 1.171 ± 0.210 and 1.436 ± 0.524	RHI was influenced by vascular tone and resistance. RHI in obese positively related with SVR. RHI is influenced by vascular tone.
32 33 34 35 36 37 38 39 40 41 42 43	Physiological changes in blood pressure (BP) impact peripheral endothelial function during adolescence. Deda et al (19)	2015	Control study	n =90 healthy adolescents to assess normal RHI response, 14.2±1.91 years, [F/M 46/44].	No controls. Assessing association between RHI and known cardiovascular risk factors.	Mean arterial pressure significantly associated with RHI (p=0.01). Positive correlation between RHI and age in the females (r=0.33, p<0.02). RHI correlated with pubertal status in males (r=0.411, p=0.03) and females (r=0.36, p =0.03).	Physiological changes in BP significantly impact PAT results.
44 45 46 47 48 49 50 51 52 53 54	Role of insulin resistance and hyperandrogenemia in early vascular dysfunction in adolescents with PCOS. Bartz et al (20)	2015	Conference abstract	14 adolescents with PCOS (on no treatment).	7 non-PCOS. Both groups had similar age, tanner stage, race, glucose tolerance status, BMI (34.1 +/- 1.1 vs. 30.4 +/- 1.6 kg/m <sup>2</sup> ).	Despite higher peripheral and hepatic insulin resistance in adolescents with PCOS, RHI is not significantly lower when compared with controls of similar total body and abdominal adiposity.	PCOS has evidence of increased vascular inflammation. Hyperandrogenemia, as well as insulin resistance, may play an important role in modulating vascular inflammation.
55 56 57 58 59 60	Cardiovascular adaptations after 10 months of intense school-based physical training for 8- to	2018	Randomised control study	n=93 small-sided games group, 9.3+/-0.4 years. n=83 circuit strength training group, 9.3+/-0.3	n = 115 controls, 9.3+/- 0.3 years	No significant differences in RHI. Pubertal status is a main predictor of RHI; positive correlation	10 months of 3 × 40 minutes/week decreased DBP and elicited discrete cardiac adaptations,

10-year-old children. Larsen et al (21)			years (10-16 years)		between Tanner stages and RHI.	suggesting intense exercise classes can have effects on cardiovascular health.
Endothelial Function in Children and Adolescents Is Mainly Influenced by Age, Sex and Physical Activity- An Analysis of Reactive Hyperemic Peripheral Artery Tonometry. Mueller et al (22)	2017	Randomised controlled study, Leipzig School Project followed over 5-year period.	n=931 RHI measurements in 445 students, age 10-17 years (baseline 11.66±0.93). n=247: 60 minutes physical exercise (PE) daily (intervention group).	n=181: 2 units of 45 minutes PE weekly (control group).	Main influential factors were age, gender and PE. RHI was higher in the intervention group by 0.09 [-0.05, 0.23]. Increase RHI from 1.53±0.42 in the youngest to 1.96±0.59 in the oldest students. This increase adjusted by age and sex was estimated as 0.11 [0.08, 0.14] per year.	If RH-PAT is used in research in adolescents, the shown age- and sex-dependence of RHI have to be taken in account.
Reactive hyperaemia index and detection of endothelial dysfunction in children with familial hypercholesterolemia (FH). Jehlicka et al(23)	2015	Conference abstract	n=24 with FH, 13.9±/-2 years. Biochemical markers of endothelial function were assessed.	n=17 healthy controls, 15.2±/-2.2 years	Significantly lower RHI in FH group (1.63±/-0.50 and 2.03±/-0.54; p<0.05). Lower RHI and elevated E-selectin in children with FH.	Possible relationship of ED in children with FH, highlighting the importance of early detection of ED when the atherosclerotic process is still reversible.

Supplementary Table 1: Endo-PAT 2000 in paediatric patients with metabolic syndrome (24 studies) including obesity, type 2 diabetes (T2D) and hypercholesterolemia. Reactive hyperemia index (RHI), augmentation index (AIx) (vascular stiffness), freeze-dried strawberry powder (FDSP), non-alcoholic fatty liver disease (NAFLD), endothelial dysfunction (ED), overweight (OW), familial hypercholesterolaemia (FH), waist circumference (WC), C-type natriuretic peptide (CNP), Laser-Doppler Flowmetry (LDF).

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# PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			Page
Title	1	Identify the report as a systematic review.	2
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Tables
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analyses, meta-regression).	N/A
13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias(s)).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6



# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Flow diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Nil
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 1-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16
	23b	Discuss any limitations of the evidence included in the review.	17
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	20
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	No response
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Prospero – no response
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Nil
Competing interests	26	Declare any competing interests of review authors.	Nil
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	With authors

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Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71  
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# SEARCH PLANNING FORM

Use this form to identify/clarify the key concepts and the scope of your research topic

**DATE RECEIVED: 08/02/2021**

**DATE SEARCH COMPLETED: 03/03/2021**

## YOUR RESEARCH TOPIC

Paediatric arterial tonometry on children with any condition or healthy children.

## PICO AND SEARCH TERMS

Patient/Population and/or problem	Exposure	Outcomes	Study type	Search limits
Under 16's	Peripheral Arterial tonometry		All studies	Under 16 only From 2015 to current

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## SOURCES TO SEARCH

Resources	Number of results	Date searched
Cochrane	30	03/03/2021
Embase	123	03/03/2021
Medline EBCSO	56	03/03/2021
Pubmed	61	03/03/2021
Cinahl	20	03/03/2021
<b>Total</b>	<b>290</b>	
<b>Total after deduplication</b>	<b>158</b>	

## SEARCH STRATEGY

<b>Population</b>	exp adolescent/ or exp child/ OR exp pediatrics/ OR (ado* or child* or preschool* or schoolboy* or schoolgirl* or boy or boys or girl or girls or teen* or toddler*).ab,ti,tw. OR (infant or infants or baby or babies or "pre-school").ab,ti,tw. OR (pediatric* or paediatric*).ab,ti,tw.
<b>Intervention</b>	exp *peripheral arterial tonometry/ OR (peripheral adj3 tonometry).ab,ti,tw. OR exp peripheral arterial tonometry/ OR (PAT adj2 (analys* or test*)).ab,ti,tw. OR endopat.ab,ti,tw.
<b>Outcomes</b>	
<b>Date filter</b>	2015 to current

# BMJ Open

## Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic review.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062098.R1
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2022
Complete List of Authors:	Hayden, Jenny; RCPI O'Donnell, Gill; University Hospital Limerick, Department of Paediatrics deLaunois, Isabelle; University of Limerick O'Gorman, Clodagh; Graduate Entry Medical School, University of Limerick, Paediatrics; University Hospital Limerick,
<b>Primary Subject Heading</b>:	Paediatrics
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice, Nutrition and metabolism, Sports and exercise medicine, Medical management
Keywords:	PAEDIATRICS, Community child health < PAEDIATRICS, Paediatric endocrinology < PAEDIATRICS, EDUCATION & TRAINING (see Medical Education & Training), Change management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisational development < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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14 5 **Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic**  
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16 6 **review.**  
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46 17 **Key words:** Endo-PAT 2000, peripheral artery tonometry, Endothelial dysfunction, paediatric  
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48 18 diabetes mellitus, chronic diseases  
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51 19 **Word count:** 3881  
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3 **23 Abstract:**  
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6 **24 Objectives:** Endo Peripheral Artery Tonometry (EndoPAT-2000) is a non-invasive technology for  
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8 **25** measuring endothelial dysfunction (ED). The reactive hyperaemia index (RHI) is resulted and is low  
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10 **26** when ED is present. We aim to synthesise the literature on paediatric ED that utilised Endo-PAT  
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12 **27** analysis.  
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15 **28 Design:**  
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18 **29** A comprehensive systematic review was conducted from January 2015 to March 2021. The databases  
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20 **30** included Cochrane, MEDLINE EBSCO, EMBASE (Ovid), PUBMED and CINAHL EBSCO.  
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22 **31** Exclusion criteria were: 1. If a study used a different device for example. 2. If the study had no  
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24 **32** results. Inclusion criteria were: 1. Published in the English; 2. More than 50% of study subjects were  
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26 **33** in the paediatric age range; 3. Data relevant to paediatric age range children could be extrapolated  
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28 **34** from all data, where not all study subjects were children.  
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31 **35 Results:**  
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34 **36** Following the removal of duplicates, 156 articles were initially identified . Following exclusion, 50  
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36 **37** articles were included for review. We have subdivided these papers into different systems for ease of  
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38 **38** reference and have reported our findings in 6 tables: patients with type 1/2 diabetes, obesity,  
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40 **39** cardiovascular, respiratory, psychiatric conditions and miscellaneous diseases. For each, the study  
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42 **40** design, population, control group (if available), RHI results and conclusions were reported.  
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45 **41 Conclusions:**  
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48 **42** A number of papers using Endo-PAT for children with various chronic diseases have evidence of ED.  
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50 **43** However, in many cases, there has only been a single cohort study using Endo-PAT. Further studies  
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52 **44** are required to validate these findings and to help characterise the cardiovascular risk profile of  
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54 **45** children with chronic disease. Further studies are also required that will characterise more completely  
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56 **46** the cardiovascular risk profile of these children.  
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3 47 Consensus on other vascular risk markers that could be included in future studies is ideal and if  
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5 48 accomplished, this would facilitate meta-analyses of studies of relatively rare conditions.  
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52 **Strengths and limitations:**

- 53     • Comprehensive systematic review to synthesise the literature on endothelial dysfunction  
54       using Endo-PAT in paediatric patients..  
55     • All study types were reviewed and even the studies without results but were relevant were  
56       included in our discussion.  
57     • In many cases, there has only been a single cohort study using Endo-PAT for a particular  
58       disease  
59     • Separate paediatric results were obtained where possible from studies with combined adult  
60       and paediatric data; however, some papers were of poor quality and had limited results  
61       available  
62     • Only papers from January 2015 to March 2021 were included in our review.  
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65 **Introduction:**

66 Endothelial dysfunction (ED) is an early predictor of cardiovascular disease(1). ED occurs when the  
67 endothelium loses its ability to promote vasodilation, fibrinolysis and anti-aggregation(2). It can be  
68 caused by oxidative stress with loss of vaso-active or inflammatory homeostasis within the body's  
69 vascular system. It may be secondary to mechanical stimuli, for example increased intraluminal  
70 pressure within the blood vessel or metabolic factors such as hormones (oestrogen's vasodilation  
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3 71 action)(3). Damaged endothelium can release a cascade of substances which pose a risk of  
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5 72 thrombosis, inflammation and ultimately atherosclerosis(4).  
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8 73 ED in paediatric populations has been associated with several conditions including type 1 diabetes  
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10 74 (T1D), type 2 diabetes (T2D), renal impairment, obesity and metabolic syndrome(5-8). ED can  
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12 75 progress to atherosclerosis which is a chronic condition that poses severe risk of certain diseases  
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14 76 including coronary artery disease, stroke and peripheral arterial disease.  
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17 77 Improving glucose control can protect endothelial function. Persistent high sugars can impair  
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19 78 endothelial function via oxidative stress and production of free-radicals(2). Diabetic microangiopathy  
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21 79 can result in the outcomes of retinopathy, neuropathy and peripheral vascular neuropathy. Subclinical  
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23 80 evidence of these complications can be seen in paediatric patients, especially in those with poor  
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25 81 glycaemic control. In patients with T2D, obesity and metabolic syndrome, insulin resistance is one of  
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27 82 the most importance factors contributing to ED(8). Metabolic syndrome is a pro-inflammatory state  
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29 83 where dyslipidaemia, hyperuricemia, and hypertension occur and can predispose to ED(9).  
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31 84 Unfortunately, there have been reports of T2D paediatric patients diagnosed with microangiopathic  
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33 85 complications, particularly nephropathy(10). This early endothelial damage can be linked with  
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35 86 increased morbidity and mortality(11). New onset diabetes after transplantation (NODAT) is  
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37 87 characterised by insulin resistance and T2D(12).  
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41 88 In recent decades, the number of childhood cancer survivors is increasing(13). Treatments utilized  
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43 89 such as haematopoietic stem cell transplantation have increased risk of cardiovascular disease(14, 15).  
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45 90 Following chemotherapy, radiotherapy, immunosuppressive treatments the risk of insulin resistance  
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47 91 has been noted(16). With advances in treating malignant paediatric conditions there are long term  
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49 92 complications emerging in survivors. High dose chemotherapy including anthracyclines, alkylating  
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51 93 agents and vinca alkaloids may disrupt the substances on the surface of the endothelium and impair its  
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53 94 ability to dilate and constrict. Moreover, total body radiation poses a risk by damaging the elastic  
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55 95 matrix. Heart disease in long-term cancer survivors is 5-10 times higher than their siblings(16).  
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3 **97 Endo-PAT 2000:**  
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6 **98** Endo Peripheral Artery Tonometry (Endo-PAT 2000) is a non-invasive technology for measuring ED  
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8 **99** developed by Itamar Ltd. Non-invasive pneumatic probes which are placed on the both index fingers,  
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10 **100** which continuously records pulse wave amplitude. A blood pressure cuff is inflated to occlude blood  
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12 **101** flow and response after deflation is recorded. The reactive hyperaemic index (RHI) is resulted  
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14 **102** following this mini-ischemic stress to the vessel. The pulse wave amplitude (PWA) is measured and  
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16 **103** computes a RHI result automatically. RHI is calculated as the ratio of average PWA divided by the  
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18 **104** average amplitude during the equilibration period. To compensate for any systemic changes, this ratio  
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20 **105** is normalized to a concurrent signal from the contralateral finger.  
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23 **106** Numerous studies in both adult and paediatric literature reveal Endo-PAT's excellent reproducibility  
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25 **107** and reliability(17, 18). In ED, the RHI is low and pulse amplitude is high. PAT also provides results  
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27 **108** on the peripheral augmentation index (PAT-AIx). Bonetti et al report a RHI of <1.35 as indicative of  
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29 **109** coronary ED in adults(19). However, there is no reported RHI cut off value in paediatric patients.  
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31 **110** Endo-PAT can be used at the patient's bedside, without extensive training required of the operator.  
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34 **111** Prior to Endo-PAT, ED had been assessed by flow-mediated vasodilation (FMD). FMD uses an  
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36 **112** ultrasound to assess the change in brachial artery diameter in response to increased flow after a period  
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38 **113** of vascular occlusion by a blood pressure cuff and is highly dependent on nitric oxide (NO)  
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40 **114** bioavailability. ED is identified by less vasodilatation (reduced FMD) of the brachial artery. FMD is  
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42 **115** technically challenging to perform, user-dependent and requires training. FMD results macro blood  
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44 **116** vessel reactivity whereas Endo-PAT results micro, which may account for the challenges in  
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46 **117** comparing the two techniques. Endo-PAT is easier to set up, is automated and less user-  
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48 **118** dependent. Wilk et al reported that RHI correlated with FMD ( $r = 0.35$ ,  $P < 0.01$ )(20) however there  
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50 **119** are other studies who have not reported a correlation between the two techniques.  
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54 **120 Objective:**  
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57 **121** The aim of this study is to conduct a systematic review to synthesise the literature on the use of Endo-  
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59 **122** PAT 2000 in paediatric populations in assessing the risk of ED in chronic diseases.  
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45 124 **Methods:**  
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8 125 A comprehensive systematic review was conducted to identify publications that investigated Endo-  
9 PAT 2000. All papers published from January 2015 to March 2021 in paediatric populations age birth  
10 126 to 16 years of age were analysed. PRIMSA study design was used.  
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15 128 The following scientific databases were searched: The Cochrane Database, MEDLINE EBSCO,  
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17 129 EMBASE (Ovid), PUBMED and CINAHL EBSCO. The search was limited by to English studies.  
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19 130 The search was limited by type of subjects (human), date (2015 to March 2021) and included all study  
20 131 types. Snowballing method was used. Authors of joint adult and paediatric papers were contacted by  
21 132 email to obtain separate paediatric data.  
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26 133 The database search was repeated several times using the combinations of keywords, MeSH terms and  
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28 134 filters (child: birth-16 years). The following MeSH terms or key words were used for searching:  
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30 135 Peripheral arterial tonometry, PAT test, endopat, adolescent, ado\*, child, paediatric, pediatric,  
31 136 preschool, schoolboy, schoolgirl, boy, girl, teen, toddler, infant, baby.  
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35 137 Exclusion criteria were: 1. If a study used a different device for example 'Watch-PAT;' 2. If the study  
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37 138 had no results. Inclusion criteria were: 1. Published in the English; 2. More than 50% of study  
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39 139 subjects were in the paediatric age range; 3. Data relevant to paediatric age range children could be  
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41 140 extrapolated from all data, where not all study subjects were children. A child was defined as up to 16  
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43 141 years, and this is consistent with PubMed's definition of a child. Where data relevant to children  
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45 142 could not be extrapolated from the whole dataset, the study authors were contacted for additional  
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47 143 information prior to study inclusion or exclusion.  
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51 144 **Patient and public involvement:**  
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53 145 No patient involved.  
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56 146 **Data collection and analysis:**  
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3 147 A total of 290 articles were obtained via the online database search (*Figure 1*: flow diagram).  
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5 148 Following removal of duplicates, 158 articles remained. The second screening was conducted by  
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7 149 'Rayyan- systematic review software.' Two further duplicate articles were removed, with 156  
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9 150 remaining for review.  
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11 151 Two independent authors separately performed a blind screen on the 156 abstracts. 65 articles were  
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13 152 initially excluded based on title or abstract: 37 adult studies, 18 'PAT' did not represent peripheral  
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15 153 arterial tonometry (e.g. prism adaptation test, psychosocial assessment tool), 6 Watch-PAT, 2 sleep  
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17 154 studies and 2 had no results available.  
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19 155 The remaining 91 articles were analysed viewing full text articles for further information. A further 20  
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21 156 were excluded as they did not fit inclusion criteria or have results to report. Some of these articles that  
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23 157 included Endo-PAT 2000 in paediatrics did not have results for the systematic review but had  
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25 158 conclusions that were relevant to the paper were referenced in the results section.  
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27 159 Twenty-eight authors of studies including both adults and paediatric patients were contacted twice by  
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29 160 email to gather separate information on the paediatric participants. Twenty authors did not reply and  
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31 161 were thus excluded. Eight authors replied: three providing results, four unable to give separate  
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33 162 paediatric data and one author's research was on adult patients so was excluded. Three of the articles  
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35 163 whose authors replied with data were included in our review. Four studies were obtained via snow  
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37 164 balling searching.  
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39 165 A total of 50 articles were included in our results and are represented in tables 1-6. For each eligible  
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41 166 study the following data was reported: author, year of publication, design of the study, population  
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43 167 studied, control group (if available), RHI results.  
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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median	Control group: n=sample size, age; mean $\pm$ SD or median	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
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			(range), [F/M]	(range), [F/M]		
Adolescents and young adults with type 1 diabetes display a high prevalence of endothelial dysfunction. Scaramuzza et al (21)	2015	Cohort prospective observational study. Results at baseline and after a 1-year follow-up	n=73 T1D adolescents, diagnosed > 1 year, 16.2 +/- 3.5 years, [F/M 25/48]	No controls.	56 (76.7%) had ED, with lower mean RHI scores (1.26 ± 0.22 versus 2.24 ± 0.48, p < 0.0001). More with ED had abnormal cardiac autonomic tests (p = 0.02) and were more sedentary. After 1 year follow-up in 64/73 patients, 81.8% had ED, despite some improvement in HbA1c.	T1D adolescents had evidence of ED. Good metabolic control (HbA1c ≤7.5%) and regular physical activity might be protective. ED progression despite some improvement to HbA1c.
Alpha-Lipoic Acid and Antioxidant Diet Help to Improve Endothelial Dysfunction in Adolescents with Type 1 Diabetes: A Pilot Trial. Scaramuzza et al (22)	2015	Double-blind, randomized controlled trial – snowballing. Results at baseline and after follow-up	n=71 T1D patients, followed for at least 1 year, age 16.3 ± 3.4 years, [F/M 29/42]. (a) antioxidant diet 10,000 ORAC + alpha-lipoic acid; (b) antioxidant diet 10,000 ORAC + placebo;	(c) controls .	3 double-blind study arms: (a) antioxidant diet 10,000 ORAC + lipoic acid: RHI 1.40 ± 0.68 vs 1.72 ± 0.66 (P<0.05) (baseline vs after 6 months). (b) antioxidant diet 10,000 ORAC + placebo: RHI 1.39 ± 0.41 vs 1.58 ± 0.40 (P>0.05) (c) Controls: RHI 1.58 ± 0.64 vs 1.54 ± 0.42 (P>0.05).	Improved RHI with alpha-lipoic acid in T1D patients.

Effect of metformin on endothelial function in overweight adolescents with type 1 diabetes (T1D). Nadeau et al(23)	2016	Conference abstract. Endo-PAT scores at baseline and 13 weeks.	Total n=70 overweight T1D patients. n= 41 on metformin (up to 2000 mg/day), 12-19 years (mean 15.8)	n=29 placebo group.	Mean baseline RHI 1.8 +/- 0.6 in metformin group and 1.7 +/- 0.6 placebo group. At 13 weeks, no significant change from baseline RHI (+0.1 in metformin vs. -0.0 in placebo, P = 0.08). There was some improvement in endothelial function among males.	No significant RHI change with metformin overall but some improvement in overweight T1D males.
Assessment of biomarkers of inflammation and premature atherosclerosis in adolescents with type-1 diabetes mellitus. Babar et al (24)	2019	Cross-sectional study	T1D adolescents ≥12 years. Two groups based on different HbA1c ranges. (a) HbA1c ≥9.5% (n=25)	(b) HbA1c ≤8.5% (n=27).	PAT results were not significantly different between the groups. Pearson correlation showed a significant direct relationship between rising HbA1c and PAT (p=0.03, r=0.31).	Suboptimal glycemic control (rising HbA1c) causes early atherosclerosis.
Improvements in peripheral vascular function with vitamin D treatment in deficient adolescents with type 1 diabetes. Deda et al (25)	2018	Research article – snow balling. Tested at two different time points.	n=21 T1D patients followed for ~2 years. 25-OH-Vit. D levels < 37.5 nmol/L. Age 15.7 ± 1.4 years, [F/M 19/12]	Controls: matched age, sex and T1D.	After 4.8 ± 1.3 months of Vit. D supplementation RHI improved: 1.83 ± 0.42 vs 2.02 ± 0.68 (P<0.05).	Vit. D supplementation associated with improvement to endothelial function and reduced urinary inflammatory

						markers.
Non-alcoholic Fatty Liver Disease in Hispanic Youth with Dysglycemia: Risk for Subclinical Atherosclerosis? Bacha et al (26)	2017	Cross-sectional study	n=23 overweight/obese with NAFLD, age 15.2 ± 0.5 years. n=12 prediabetes, n=11 T2D, [F/M 13/10]	n=13 overweight/obese without NAFLD, age 15.7 ± 0.4 years. n=8 pre-diabetes, n=5 T2D, [F/M 3/10]	NAFLD group had lower RHI (1.4 ± 0.05 vs 1.7 ± 0.09, p= 0.002), greater AIx (-6.0 ± 1.6 vs -12.0 ± 2.1, P = 0.03). Hepatic fat is inversely related to RHI (r = -0.49, P = 0.002) and positively related to AIx (r = 0.45, P = 0.006).	Hepatic fat and AST/ALT levels inversely related to RHI. If dysglycemia, NAFLD is associated with worse ED.
Endothelial function in youth: A Biomarker modulated by adiposity-related insulin resistance. Tomsa et al (27)	2016	Cross-sectional study	Total n = 60. n=25 obese without DM, n=19 obese with impaired glucose tolerance, n=16 obese T2D but HB1Ac < 8%. Age 15.5 (0.2), [F/M 37/23]	n=21 normal weight, age 15.5 (0.2), [F/M 9/12]	RHI inversely related to % body fat (r = -0.29, P = .008), total (r = -0.37, P = .004), subcutaneous (r = -0.39, P = .003), and visceral abdominal fat (r = -0.26, P = .04). AIx at heart rate 75 bpm was higher (worse) in the lower RHI groups (P = .04).	Childhood obesity is associated with ED (lower RHI and higher AIx). RHI lower in obese and T2D. RHI negatively related with percentage body fat, WC, Leptin, TNF-alpha, blood glucose.
Circulating fibroblast growth factor-21 (FGF-21): A biomarker of subclinical atherosclerosis in obese youth with non-alcoholic fatty liver disease (NAFLD)? Bacha et al (28)	2017	Conference abstract	Obese adolescents with NAFLD, 15.4+/-0.3 years. n=13 normal glucose tolerance,	Control group: no NAFLD. No difference in age/gender between groups.	Lower RHI in NAFLD group and higher AIx-75. FGF-21 concentrations were related to RHI (r=-0.33,	Increased FGF-21 in obese adolescents with NAFLD and associated with

			n=19 prediabetes, n=16 T2D patients		p=0.03) and AIx (r=0.45, p=0.02).	insulin sensitivity and ED. FGF-21 may constitute a biomarker ED.
Assessment of Microvascular Function in Children and Adolescents with Diabetes and Obesity. Kochummen et al(29)	2019	Cross- sectional study	DM group. n=33 T1D with normal weight. n=8 obese T2D, age 12.7 (3.8) years, [F/M 25/16]	n=17 obese, non-DM children (normal BGL, BP and lipid profile), 12.8 (2.7) years, [F/M 9/8]	For every 1% increase in HbA1C, RHI decreased by 0.097 (P = 0.01). RHI of DM group with HbA1C <10% ( $1.70 \pm 0.58$ ) versus those with $\geq 10\%$ ( $1.21 \pm 0.19$ ) (p= 0.02).	Poorly-controlled DM (HbA1C $\geq$ 10%) had lower RHI. RHI negatively related with HbA1C. RHI similar between obese and normal weight with T1D. Similar between T1D and T2D.
Free Vitamin D: Relationship to Insulin Sensitivity and Vascular Health in Youth. Bacha et al (30)	2019	Cross- sectional study. Comparison across tertiles of free 25(OH)D concentratio ns	n=79, age $15.4 \pm 0.2$ years, [F/M 45/34]. n=30 overweight. n=31 overweight with prediabetes	n=18 normal weight and normal glucose tolerance.	The lowest tertile group had lower RHI ( $1.42 \pm 0.06$ , $1.54 \pm 0.06$ , and $1.77 \pm 0.09$ , P = 0.002), compared with the second and third tertiles.	Youth with low free 25(OH)D or BioD concentrations have lower insulin sensitivity and worse endothelial function.
Urine Albumin-to- Creatinine Ratio (UACR): A Marker of Early Endothelial Dysfunction in Youth. Bartz et al(31)	2015	Control study. Fasting UACR analysed.	n=25 overweight (OW) with normal glucose tolerance, $15.6 \pm$ 0.2 years, [F/M	n=13 normal weight, $16.3 \pm$ 0.4, [F/M 7/6].	Normal weight group RHI $1.84 \pm 0.1$ . OW with normal glucose tolerance $1.56 \pm 0.1$ . OW with prediabetes	UACR is an early marker of endothelial dysfunction in youth,

			17/8]. n=20 OWwith prediabetes, [F/M 11/9].		1.56 ± 0.1 (P = .04). UACR was related to RHI (r = -0.33, p = .01).	independent of glycemia.
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169 Table 1: Total of 11 studies included. Endo-PAT 2000 in paediatric type 1 diabetes mellitus (T1D) patients (5  
170 studies), type 2 diabetes and prediabetes (6 studies). Reactive hyperemia index (RHI), type 1 diabetes mellitus  
171 (T1D), type 2 diabetes mellitus (T2D), augmentation index (AIx) (vascular stiffness), endothelial dysfunction  
172 (ED), Oxygen radical absorbance capacity units (ORAC), non-alcoholic fatty liver disease (NAFLD),  
173 overweight (OW), Urine Albumin-to-Creatinine Ratio (UACR).

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<b>Title, lead author</b>	<b>Year</b>	<b>Study design</b>	<b>Population: n=sample size, age; mean ± SD or median (range), [F/M]</b>	<b>Control group: n=sample size, age; mean ± SD or median (range), [F/M]</b>	<b>Results: RHI reported. If RHI not specified, we reported p/r values</b>	<b>Outcomes</b>
Effects of a dietary strawberry powder on parameters of vascular health in adolescent males. Djurica et al (32)	2016	Randomised, double-blind, cross-over study	n=15 OW/obese males, 14-18 years (mean 16). 1-week daily 50g of freeze-dried strawberry powder (FDSP) or control powder. Before/after plasma nitrate/nitrite	10 control powder, 14-18 years (mean 16).	Acute plasma nitrate/nitrite levels increased 1 h after consuming the FDSP (P<0.001). When nitrate levels increased after FDSP intake compared to controls, had an increase in RHI (P=0.014).	Strawberries can provide vascular health benefits to OW/obese adolescent males.

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			levels measured.			
Flow-mediated dilation in obese adolescents: Correlation with waist circumference (WC) and systolic blood pressure (SBP). Hussid et al (33)	2018	Case control study	n=20 obese patients, median age 14 years	n=10 normal weight, median age 15 years, paired for gender	No RHI difference between groups. 35% obese group had metabolic syndrome, none in control group. OSA in 86.6% obese and 50% of normal weight group.	Obese group had evidence of ED and metabolic syndrome. Increased WC and SBP seem to be related to this finding.
Improvement of microvascular endothelial dysfunction induced by exercise and diet is associated with microRNA-126 in obese adolescents. Donghui et al (34)	2019	Quasi-randomized study	n=57 obese male adolescents, 12-18 years, [F/M = 0/57], 6-week exercise program with dietary intervention.	n=10 normal weight adolescents, 15.38 ± 2.82 years, [F/M 0/10], maintained sedentary	Obese group RHI 1.43 (0.35) vs controls 1.67 (0.36) (p<0.05). After 6 weeks intervention RHI increased (p<0.01) and microRNA-126 decreased (p<0.01). miRNA-126 positively correlated with ΔRHI (r = 0.69, p<0.05).	RHI improved in obese group after exercise and diet interventions. Findings might be related to changes in serum miRNA-126.
Distribution of peripheral arterial stiffness and endothelial function as well as their correlations with cardiovascular	2016	Cross-sectional population-based study, conference abstract	n=94 obese, 7-17 years, used automatic waveform analyser (BP-203RPE-I) and Endo-PAT 2000.	n=452 normal-weight	In normal weight group, RHI increased with age (r=0.33, P<0.01; r=0.36, P<0.01). RHI positively correlated with BMI (r=0.10, P=0.018) but	Brachial-ankle pulse wave velocity (baPWV) and RHI increased along with age; arterial stiffness and endothelial function



risk factors in children and adolescents. Mu et al (35)					negatively correlated with DBP ( $r=-0.10$ , $P=0.016$ ). RHI did not differ between genders.	continued to develop in the normal weight group.
Urinary biomarkers as indicator of chronic inflammation and endothelial dysfunction in obese adolescents. Singh et al(36)	2017	Control study, research article	n=63 total. n=14 overweight (OW), n=29 obese, age 13.8 (2.4), [F/M 23/20]	n=20 normal weight (NW), age 13.9 (2), [F/M 8/12]	There were no differences in RHI levels: NW 1.6 (0.1), OW 1.66 (0.1) and obese 1.67(0.1). NW girls RHI 1.9 vs NW boys 1.25.	No significant correlation between RHI and urinary markers. RHI higher in NW female adolescents.
Prevalence of Type D personality in obese adolescents and associated cardiovascular risk. Bruyndonckx et al(37)	2018	Control study, conference abstract	Obese adolescents-no definite numbers	Healthy normal weight children	Positive correlation in obese adolescents between negative affectivity and vascular stiffness ( $r= 0.28$ ; $p=.04$ )	Obese adolescents have worse cardiovascular risk profile with ED.
Endothelial function and arterial stiffness in obese adolescents - A relation to baroreflex function. Czippelova et	2017	Conference abstract	n=22 obese, 15.28 +/- 2.8 years, [F/M 10/12]	n=22 non-obese, 15.98 +/- 2.46 years, [F/M 10/12]	No significant difference in RHI ( $p = 0.473$ ). Baro-reflex sensitivity was also calculated.	No difference in RHI between groups. Findings require further study.

al(38)						
Obesity in children and adolescents: A relation to endothelial function and arterial stiffness. Czippelova et al(39)	2016	Conference abstract	n=16 obese adolescents, 15.22 +/- 2.2 years, [F/M 7/9]	n=16 non-obese, 16.22 +/- 1.5 years, [F/M 7/9]	Significant difference in RHI (p = 0.018) with RHI higher in obese group (1.66 +/- 0.28 vrs 1.4 +/- 0.25).	Less early atherosclerotic changes in obese group which was in contrast to expectations. Findings require further study.
Preclinical vascular alterations in obese adolescents detected by Laser-Doppler Flowmetry technique. Fusco et al (40)	2020	Research article	n=22 obese adolescents, 14.11 +/-2.53, [F/M 13/9]	n=24 normal-weight, 15.2 +/- 1.56, [F/M 11/13]	Similar RHI between obese and non-obese groups (1.80 +/- 0.62 and 1.86 +/- 0.51).	RHI not different between groups. RHI did not correlate with LDF. LFD detected preclinical vascular dysfunction by impaired skin microcirculation.
Impaired endothelial function in adolescents with overweight or obesity measured by peripheral artery tonometry. Pareyn et al (41)	2015	Cross sectional study	n=27 overweight (OW)/obesity, 14.7 (13.0–16.4) years, [F/M 11/16]	n=25 normal weight controls, 15.5 (13.9–16.2) years, [F/M 13/12]	RHI normal weight 1.88 (1.7-2.4) vs OW/obese 1.5 (1.3-1.9) (P< 0.05). Lower RHI if OW /obese and higher baseline pulse amplitude (p = 0.027 and p < 0.0001). RHI positively	ED and higher baseline pulse amplitude in OW group. First time literature reports significant difference in baseline pulse amplitude

					correlated with age and tanner stage ( $P < 0.05$ ). RHI negatively correlated with DBP ( $P < 0.05$ ).	between OW adolescents compared to peers.
C-type natriuretic peptide (CNP) plasma levels and whole blood mRNA expression show different trends in adolescents with different degree of endothelial dysfunction. Del Ry et al(42)	2020	Research article -snow balling	n=16 primary obesity, not DM, age 13.3 (0.5) years, [F/M 8/8].	n=24 normal weight, age 14.3 (0.4) years, [F/M 14/10].	RHI normal weight 2.1 (0) vs obese 1.4 (0) ( $P < 0.005$ ). RHI negatively associated with CNP and diastolic BP ( $P < 0.005$ ).	RHI significantly lower in obese group. RHI negatively related with CNP, DBP, fat mass and HbA1C.
C-type natriuretic peptide (CNP) is closely associated to obesity in Caucasian adolescents. Del Ry et al (43)	2016	Research article -snow balling	n=10 overweight, age 12.8 (1.6) years, [F/M 5/5]. n=45 obese, 12.8 (1.6) years, [F/M 19/26]	n=27 normal weight, age 12.8 (1.4) years, [F/M 14/13]	Normal weight group RHI 2.1 (0.2) vs OW 1.6 (0.4) ( $P < 0.05$ ). Normal weight vs obese group RHI 1.4 (0.3) ( $P < 0.005$ ). RHI negatively associated with CNP ( $P < 0.005$ ).	RHI significantly lower in overweight/obese groups. CNP negatively related with RHI.
Arterial Stiffness and Endothelial Function in Young Obese Patients - Vascular Resistance Matters. Czippelova et al (6)	2019	Research article	Author contacted for separate paediatric data. n=16 obese group, age <16 years,	n=15 controls, age <16 years, [F/M 7/8]	RHI control vrs obese groups: $1.320 \pm 0.427$ and $1.457 \pm 0.280$ . RHI obese girls and boys: $1.410 \pm 0.253$ and	RHI is influenced by vascular tone and resistance. RHI in obese positively related

			[F/M 7/9]		1.494 ± 0.308. RHI control girls and boys: 1.171 ± 0.210 and 1.436 ± 0.524	with SVR.
Cardiovascular adaptations after 10 months of intense school-based physical training for 8- to 10-year-old children. Larsen et al (44)	2018	Randomised control study	n=93 small-sided games group, 9.3+/-0.4 years. n=83 circuit strength training group, 9.3+/-0.3 years (10-16 years)	n = 115 controls, 9.3+/-0.3 years	No significant differences in RHI. Pubertal status is a main predictor of RHI; positive correlation between Tanner stages and RHI.	10 months of 3 × 40 minutes/week decreased DBP and elicited discrete cardiac adaptations, suggesting intense exercise classes can have effects on cardiovascular health.

177 Table 2: Endo-PAT 2000 in paediatric patients who are overweight (OW)/obese (14 studies). Reactive  
 178 hyperemia index (RHI), augmentation index (AIx) (vascular stiffness), freeze-dried strawberry powder (FDSP),  
 179 endothelial dysfunction (ED), overweight (OW), normal weight (NW), waist circumference (WC), C-type  
 180 natriuretic peptide (CNP), Laser-Doppler Flowmetry (LDF).

Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Nocturnal blood pressure dipping as a marker of endothelial and	2020	Cross-sectional study – author	n=20, 9-19 years (mean 16.5), (7 were age 16 or under). Average	Separated into 2 groups based on nocturnal BP dipping status.	Mean ln(RHI) for n=7 (aged 16 and under): 0.529. 22% had ED. Reduced	Isolated nocturnal BP non-dipping is associated with ED and atherosclerotic

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cardiac function in pediatric-onset systemic lupus erythematosus (SLE). Chang et al (7)		contacted for separate paed data	disease duration 3.2 years ( $\pm$ 2.1). [F/M 17/3]		diastolic BP dipping was associated with poorer endothelial function (r 0.5, p = 0.04).	changes. Potential role for routine ABPM for youth with SLE.
Physiological changes in blood pressure (BP) impact peripheral endothelial function during adolescence. Deda et al (45)	2015	Control study. Assessing association between RHI and known cardiovascular risk factors.	n =90 healthy adolescents to assess normal RHI response, 14.2 $\pm$ 1.91 years, [F/M 46/44].	No controls	Mean arterial pressure significantly associated with RHI (p=0.01). Positive correlation RHI and age in females (r=0.33, p<0.02). RHI correlated with pubertal status: males (r=0.411, p=0.03), females (r=0.36, p=0.03).	Physiological changes in BP significantly impact RHI results.
Endothelial Function and Arterial Stiffness Relate to Functional Outcomes in Adolescent and Young Adult Fontan Survivors. Goldstein et al (46)	2016	Cross-sectional prospective observational study	n=60, 8-25 years (mean 13.9 $\pm$ 4.1), [F/M 29/31]	No controls	AIx (P<0.05) negatively associated with peak VO2. PAT derived baseline pulse amplitude (P<0.05) negatively associated with minute ventilation to CO2 ratio. PAT-AIx (P<0.05) negatively associated with parent-reported Paeds QOL total and physical health scores.	Worse vascular measures associated with worse functional measures. Increased arterial stiffness and decreased endothelial function are associated with lower aerobic capacity, physical activity, and QOL in Fontan survivors.

<p>Natural history of vascular function in adolescent and young adult Fontan survivors: A longitudinal assessment of endothelial function and arterial stiffness. Goldstein et al (47)</p>	2017	<p>Prospective single-centre longitudinal study, conference abstract. Paired testing at a mean interval of 2.0 +/- 0.2 years of Fontan survivors.</p>	<p>n=50, mean 13.7 +/- 4.2 years, [F/M 23/27]</p>	No controls	<p>Decreases in RHI (0.002 +/- 0.01/yr) were not significant. AIx improved by 0.74 +/- 0.3/yr (p=0.02). Changes RHI and AIx did not correlate with peak VO changes. BMI was a predictor for RHI (R 0.17, p=0.007). Change in resting O2 saturation was the only predictor of change in AIx (R 0.09, p=0.04).</p>	<p>Vascular function does not change uniformly in Fontan survivors. Changes in vascular function do not relate to changes in aerobic capacity but are associated with changes in anthropometric measures and O2 saturation.</p>
<p>Vascular function long term after Kawasaki disease: another piece of the puzzle? Pinto et al (48)</p>	2017	<p>Single-centre prospective study</p>	<p>n=43 Kawasaki patients, age &gt;11 years, diagnosed &gt;5 years ago, with no coronary lesions or any other risk factors for cardiovascular disease.</p>	<p>n= 43 control group of individuals without cardiovascular risk factors.</p>	<p>Kawasaki patients had decreased RHI compared with controls (1.59±0.45 versus 1.98±0.41; p&lt;0.001). AI was similar in both groups (-4.5±7 versus -5±9%; p 0.6).</p>	<p>Children with Kawasaki disease may have long-term sequelae, even when there is no detectable coronary artery involvement in the acute stage of disease.</p>
<p>Endothelial function in children with a history of Henoch Schonlein purpura (HSP). Butbul Aviel et al (49)</p>	2017	<p>Observational prospective study</p>	<p>n=19 with HSP, 13.5 ± 3.9 years, [F/M 8/11]</p>	<p>n=23 healthy children, 12.8 ± 4.5 years, [F/M 7/16]</p>	<p>Mean RHI 1.81 study group and 1.87 control group (p = 0.18). RHI higher in patients who had endothelial function measured &gt;6 years since HSP</p>	<p>This study suggests that HSP causes short term endothelial dysfunction that improves with time.</p>

					diagnosis compared with <6 years (1.98 ± 0.74 vs. 1.38 ± 0.43 P = 0.037).	
Reactive hyperaemia index and detection of endothelial dysfunction in children with familial hypercholesterolaemia (FH). Jehlicka et al(50)	2015	Conference abstract	n=24 with FH, 13.9+/-2 years. Biochemical markers of endothelial function were assessed.	n=17 healthy controls, 15.2+/-2.2 years	Significantly lower RHI in FH group (1.63+/-0.50 and 2.03+/-0.54; p<0.05). Lower RHI and elevated E-selectin in children with FH.	Possible relationship of ED in children with FH, highlighting the importance of early detection of ED when the atherosclerotic process is still reversible.

182 Table 3: Endo-PAT 2000 in paediatric patients with cardiac and vascular conditions (7 studies). Reactive  
 183 hyperemia index (RHI), waist circumference (WC), systolic blood pressure (BP), augmentation index (AI), peak  
 184 VO (peak O<sub>2</sub> consumption), quality of life (QOL), systemic lupus erythematosus (SLE), ambulatory blood  
 185 pressure monitoring (ABPM), quality of life (QOL), Henoch Schonlein purpura (HSP), familial

Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Vascular function in asthmatic children and adolescents.	2017	Cross-sectional controlled study	n=19 asthmatic patients, age 13.6 ± 0.6 years. [F/M 0/19]	n=18 controls. 14.9 ± 0.7 years. [F/M 0/18]	LnRHI were similar between groups (p = 0.23). The augmentation index	The increased AIX@75 without changes in LnRHI in asthmatic patients

186 hypercholesterolaemia (FH).

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Augusto et al (51)					(AIx@75%) was significantly higher in the asthmatic group ( $-7.75 \pm 1.7$ ) compared to the control group ( $-15.25 \pm 1.8$ ), $p < 0.04$ .	could mean that an early detection of vascular impairment may precede ED.
The effect of weight loss on endothelial function and sleep disordered breathing (SDB) in obese children. Ysebaert et al(52)	2018	Conference abstract. Reassessed after 6-month weight loss programme.	n=62 obese, age 11-19 (mean 15.8) years, [F/M 20/42]	No controls.	Endo-Pat used. At baseline 39% had SDB. After 6 months, 86% had resolution of earlier diagnosed SDB. All showed significant improvement of endothelial function after programme ( $p < 0.001$ ). No correlations between presence of SDB and improvement in endothelial function found.	Endothelial function significantly improves after weight loss.
Polysomnographic correlates of endothelial function in children with obstructive sleep apnoea (OSA). Zhang et al (53)	2018	Cross sectional study	n=121 mild OSA, $6.2 \pm 1.6$ years, [F/M 37/84]. n=127 moderate-severe OSA, $6.0 \pm 1.6$ years, [F/M 31/96]	n=107 primary snorers (PS), age $6.4 \pm 1.8$ years, [F/M 37/70]	OSA groups lower RHI than PS ( $P < 0.001$ , $P = 0.001$ ). RHI positively correlated with age ( $r = 0.17$ , $P = 0.002$ ), BMI z score ( $r = 0.14$ , $P = 0.008$ ) and oxygen saturation ( $r = 0.15$ , $P = 0.006$ ).	Children with OSA are at increased risk for abnormal endothelial function than habitually snoring children.
Endothelial	2020	Cross	n=248 OSAS, age	n=107 primary	OSAS had lower RHI	OSAS have

dysfunction in children with obstructive sleep apnoea syndrome (OSAS). Xu et al(54)		sectional study	3-11 years	snorers (PS). No significant differences in age/gender.	1.1±0.1 vrs 1.2±0.2 (P<0.01). RHI independently correlated with age, gender, obstructive apnoea hypopnea index, oxygen desaturation index (P<0.01).	significant ED compared with PS. Frequent arousals due to obstructive respiratory events during sleep may be a candidate risk factor for ED.
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188 Table 4: Endo-PAT 2000 in paediatric patients with respiratory conditions (4 studies). Natural logarithm of RHI  
 189 (LnRHI), endothelial dysfunction (ED), reactive hyperaemia index (RHI), augmentation index (AIx), heart rate-  
 190 corrected augmentation index (AIx@75), primary snorers (PS), obstructive sleep apnoea (OSA), obstructive  
 191 sleep apnoea syndrome (OSAS).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Do self-reported stress and depressive symptoms effect	2018	Longitudinal cohort study. LOOK longitudinal study	n=203, 7.6 ± 0.3 years, [F/M 111/92].	No controls.	All relationships occurred in the hypothesised direction, but no cross-sectional	Contrast to previous findings in adolescents, little evidence between current or previous psychosocial stress or depression and endothelial function in 16-year-old

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endothelial function in healthy youth? The LOOK longitudinal study. Olive et al(55)		, who were followed through to adolescence (16 years).			or prospective evidence of early psychological stress or depression was associated with ED (all $p > 0.05$ ).	adolescents.
Cerebrovascular reactivity is associated with peripheral endothelial function (EF) among adolescents. Urback et al(56)	2016	Conference abstract	n=11 with bipolar disorder. EF measured by PAT and cerebrovascular reactivity (CVR) by blood-oxygen-level dependent fMRI.	n=35 healthy controls	EF was positively correlated with CVR in grey matter ( $r=0.41$ , $p=0.012$ ), and a peak voxel in the left-medial-frontal gyrus ( $r=0.35$ , $p=0.036$ ).	Breath-hold CVR and peripheral EF are linked, suggesting that vascular function may be a multi-systemic phenotype. EF may be a potential proxy for cerebral blood vessel function with greater accessibility and lower cost than fMRI.
Retinal-vascular photography as a window into the cardiovascular and neurocognitive burden of adolescent bipolar disorder (BD). Naiberg et al (57)	2017	Cross-sectional study, author emailed for separate paediatric data-most were teenagers	n=30 with bipolar disorder, 17.97±1.86 years	n=32 healthy controls, 16.00±1.62 years	In BD group, higher endothelial function associated with higher arterio-venular ratio ( $r=0.375$ , $p=0.041$ ).	Retinal photography may help assessing cardiovascular and neurocognitive burden of BD.
Impact of psychological health on peripheral	2017	Longitudinal 3-year follow-up study.	n=162, 14.5 ± 1 years. [F/M 94/68].	No controls.	Lower peripheral endothelial function was associated with high level of anger	High amounts of negative emotions may have adverse effects on peripheral endothelial function and regulation of the HPA-axis activity. High level of self-

endothelial function and the HPA-axis activity in healthy adolescents. Chen et al(58)		Baseline and three-year follow-up.			( $\beta = -0.332, p = 0.018$ ) and disruptive behaviour ( $\beta = -0.390, p = 0.006$ ) over three years in males, but not in females, adjusted for covariates.	concept might be protective.
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197 Table 5: Endo-PAT 2000 in paediatric patients with psychiatric conditions (4 studies). Endothelial dysfunction  
 198 (ED), endothelial function (EF), cerebrovascular reactivity (CVR), bipolar disorder (BD), functional magnetic  
 199 resonance imaging (fMRI), hypothalamic-pituitary-adrenal HPA.

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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Vascular endothelial function in inflammatory bowel disease (IBD). Winderman et al(59)	2018	Case-control study	n=16 with IBD (all in clinical remission), age 16.7 $\pm$ 2.6 years, [F/M 8/7]	n=16, age 15.1 $\pm$ 2.8 years, [F/M 7/8]	RHI IBD vs controls 1.66 vs 2.02 (P =0.036). IBD group had a mean RHI within the range associated with VD risk in adults (1.67).	IBD group lower RHI compared with controls. IBD patients may need to be monitored for thromboembolic phenomena.
Endothelial health in childhood acute	2015	Case control study	n=16 ALL survivors, age 8-	n=16 healthy sibling pairs	Both groups similar in cardiovascular risk	Evidence of poorer vascular health in

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lymphoid leukaemia (ALL) survivors: pilot evaluation with peripheral artery tonometry. Ruble et al (60)			20 years (12.9+/- 0.9), [F/M 8/8].	13.8 (0.9), [F/M 10/6].	measures but survivors had lower RHI (1.54 vs. sibling 1.77; P=0.0474).	cancer survivors.
Microvascular endothelial function in Japanese early adolescents. Odanaka et al (61)	2017	Control study	n=157 healthy adolescents divided by gender. Females n=82, median age 14 (1), 13.7 ± 0.9 years	Males n= 75, median age 14 (2) years	No difference in RHI according to sex: boys and girls 1.85 ±0.6, 1.82 ±0.66 and 1.87± 0.54. RHI was significantly associated with systolic and diastolic BP, and had no correlation with anthropometric parameters and arterial stiffness markers.	RHI among adolescents were similar to those reported in previous studies on children and early adolescents.
Endothelial Dysfunction and the Effect of Arginine and Citrulline Supplementation in Children and Adolescents With Mitochondrial Diseases. Al Jasmi, et al (62)	2020	Case control study	9 participants, age 6-17 years (mean 9.6).	3-15 years (mean 9.4). Baseline endothelial dysfunction was assessed in controls.	Lower RHI with mitochondrial diseases. RHI increased with arginine or citrulline supplementation	Supplementation with NO precursors may improve ED by enhancing NO production. First study to use Endo-PAT methodology in mitochondrial diseases.

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Assessment of traditional and non-traditional risk factors for premature atherosclerosis in children with juvenile dermatomyositis (JDM) and pediatric controls. Wahezi et al (63)	2020	Retrospective controlled study	n=40 JDM, age 6-22 (mean 12.4±4.1) years, [F/M 28/12]	n=20 controls, age 12.7±3.9 years, [F/M 14/8]	RHI controls 1.43 [1.2, 1.7] and JDM 1.57 [1.2,1.9]. If controlled for lipoprotein A (atherogenic confounder), JDM patients had 41% RHI increase, thus indicating less ED compared to controls.	Rheumatological childhood disorders may be at increased risk of developing ED, but sociodemographic factors may have a greater role in developing cardiovascular disease.
Vascular Health of Children Conceived via In Vitro Fertilization (IVF). Zhang et al (64)	2019	Cross-sectional pilot study	n=17 IVF children, 10-14 years. Also used carotid ultrasound and pulse wave velocity measurements.	Compared to published norms or to historical Stanford controls	Mean Endo-PAT index in the IVF cohort was 1.66+/-0.52, 71% had abnormal values (<1.9). Mean RHI was not significantly different between IVF and controls.	Children conceived by IVF seem to have evidence of abnormal vascular health.
Endothelial dysfunction in South African youth living with perinatally acquired human immunodeficiency virus (PHIV) on antiretroviral therapy. Mahtab	2020	Case control study	n= 431 PHIV, median 14.1 (12.8, 15.5) years, [F/M 213/218]	n=93 without HIV, median 13.9 (12.1, 15.3) years, [F/M 53/40]	PHIV had higher rates of ED (50% vs 34%; P = .01); relationship persisted after adjusting for age, sex, BMI, high BP and hypercholesterolemia (RR, 1.43; P =0.02). PHIV, CD4 count, viral load and current ART	PHIV appear to have increased risk of ED. These findings have important implications as HIV has increased risk of premature CVD and complications.

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et al (65)						class were not associated with ED after adjustment.	
Soluble CD14 (sCD14) is associated with endothelial dysfunction in South African youth on ART. Dirajlal-Fargo et al (66)	2020	Case control study	n=283 perinatally acquired HIV (PHIV), 9-14 years.	n=69 age-matched without HIV	PHIVs had lower RHI despite viral suppression (RHI=1.36 vs 1.52, p<0.01). sCD14 at 24 months correlated with ED (p≤0.04). PHIV with ED, sCD14 was associated with lower RHI (β=0.05, p=0.01).	Higher sCD14 is independently associated with ED in PHIVs.	
Role of insulin resistance and hyperandrogenemia in early vascular dysfunction in adolescents with PCOS. Bartz et al (67)	2015	Conference abstract	n=14 PCOS adolescents PCOS (on no treatment).	n=7 non-PCOS. Both groups had similar age, tanner stage, race, glucose tolerance status.	Despite higher peripheral and hepatic insulin resistance with PCOS, RHI is not significantly lower when compared with controls of similar total body and abdominal adiposity.	PCOS has evidence of increased vascular inflammation. Hyperandrogenemia and insulin resistance may play an important role in vascular inflammation.	
Endothelial Function in Children and Adolescents Is Mainly Influenced by Age, Sex and Physical Activity- An Analysis of	2017	Randomised controlled study, Leipzig School Project followed over 5-year	n=931 RHI measurements in 445 students, age 10-17 years (baseline 11.66±0.93). n=247: 60 minutes physical	n=181: 2 units of 45 minutes PE weekly (control group).	Higher RHI in the intervention group: 0.09 [-0.05, 0.23]. Increase RHI from 1.53±0.42 in the youngest to 1.96±0.59 in the oldest students. This increase adjusted	If Endo-PAT is used for research in adolescents, age and sex must to be taken in account when reporting RHI results.	



Reactive Hyperemic Peripheral Artery Tonometry. Mueller et al (68)		period.	exercise (PE) daily (intervention group).		by age and sex was estimated as 0.11 [0.08, 0.14] per year.	
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202 Table 6: Endo-PAT 2000 in paediatric patients with other miscellaneous paediatric conditions (10 studies).

203 Reactive hyperemia index (RHI), augmentation index (Aix) (vascular stiffness), endothelial dysfunction (ED),  
204 inflammatory bowel disease (IBD), acute lymphoid leukaemia (ALL), nitric oxide (NO), perinatally acquired  
205 human immunodeficiency virus (PHIV), In Vitro Fertilization (IVF), soluble CD 14 (sCD14), polycystic  
206 ovarian syndrome (PCOS), physical exercise (PE).

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## 208 Results:

### 209 Endothelial dysfunction in paediatric diabetes mellitus patients (Table 1):

210 Five studies involve only type 1 diabetes (T1D) patients (Table 1). 2/5 studies reported lower RHI  
211 results in the T1D group(21, 24). One study which included only adolescent patients, reported RHI  
212 negatively correlates with impaired metabolic control and subclinical signs of autonomic  
213 neuropathy(21). They concluded that good metabolic control ( $HbA1c \leq 7.5\%$ ) and regular physical  
214 activity might be protective against ED. One study reports an improved RHI result with an alpha-  
215 lipoic acid and antioxidant diet(22). Nadeau et al reported no significant RHI change with metformin  
216 overall but some improvement in overweight T1D males(23). Barber et al report suboptimal  
217 glycaemic control causes early atherosclerosis(24). One study noted an improvement in RHI post  
218 vitamin D supplementation in T1D patients with vitamin D deficiency(25).

219 6 studies focused on type 2 diabetes (T2D) and impaired glucose tolerance or 'prediabetes.' Tomsa et  
220 al note a link between insulin resistance and obesity by utilising Endo-PAT(27). They also noted that  
221 RHI is higher if HbA1c is less than 5.5%(27). Two studies compare on Non-alcoholic fatty liver  
222 disease (NAFLD), T2D and prediabetes patients(26, 28). If dysglycemia, NAFLD is associated with  
223 worse endothelial function. Circulating FGF-21 levels are elevated in obese youth with NAFLD and

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3 224 are associated ED and therefore may be a biomarker for ED(28). Bartz et al report urine albumin  
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5 225 creatinine ratio (UACR) may be an early marker of ED independent of glycemia(31). Endothelial  
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7 226 dysfunction may mediate the link between obesity-related insulin resistance and early  
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9 227 microalbuminuria.(31). Kochummen *et al* reported a mean RHI in obese adolescents without diabetes  
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11 228 was similar to T1D and T2D patients(29). Bacha et al report lower vitamin D concentrations are  
12  
13 229 associated with lower insulin sensitivity and worse endothelial function(30).  
14  
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16 230

### 19 231 **Endothelial dysfunction and Obesity (Table 2):**

22 232 14 studies describe the use of Endo-PAT 2000 in overweight or obese patients (*Table 2*). Studies  
23  
24 233 included measurement of the following parameters: BMI, T1D, T2D, gender, pubertal stage, age,  
25  
26 234 blood pressure values, non-alcoholic fatty liver disease, obstructive sleep apnoea, insulin, plasma  
27  
28 235 glucose levels, inflammatory markers (urinary markers, CNP, micro-RNA-126, E-Selectin). In  
29  
30 236 numerous studies, RHI was significantly lower in obese groups (6, 29, 32-35, 42, 43, 69). ED may  
31  
32 237 mediate the link between obesity-related insulin resistance and early microalbuminuria(31). Exercise  
33  
34 238 and diet control improves glycolipid metabolism(44). Two studies by Czippelova et al did not find a  
35  
36 239 lower RHI in obese groups, but recommended further studies(38, 39). Noma et al (2017) report the  
37  
38 240 beneficial effects of exercise in paediatric patients and is an important message in reducing future  
39  
40 241 endothelial complications(70). Fusco et al noted pre-clinical microvascular changes in obese patients  
41  
42 242 compared to controls using LDF but noted no RHI change(40).  
43  
44

### 46 243 **Endothelial dysfunction in cardiac and vascular conditions (Table 3):**

48 244 7 studies report the use of Endo-PAT and cardiovascular conditions (*Table 3*). Lower RHI is seen  
49  
50 245 with patients with familial hypercholesterolaemia(50). Studies assess ED in patients with systemic  
51  
52 246 lupus erythematosus (SLE) and Henoch Schonlein purpura (HSP)(7, 49, 71). Negishi et al (2016) used  
53  
54 247 Endo-PAT to compare Fontan survivors and healthy controls. The Fontan patients were aged 15 to 32  
55  
56 248 years. Mean RHI 0.56+/- 0.26 in Fontan patients and 0.78+/- 0.31 in controls (p= 0.09). RHI in  
57  
58 249 Fontan patients was associated with diastolic blood pressure, heart rate and haemoglobin A1c  
59  
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3 250 level(72). Endothelial function in Fontan patients was associated with abnormal glucose tolerance and  
4  
5 251 arterial stiffness and therefore concluded that glucose regulation might be a potential target to  
6  
7 252 improve ED in this cohort. Nozaki et al (2018) assessed ED in conduit and resistance arteries and  
8  
9 253 used FMD and Endo-PAT in paediatric patients with repaired coarctation of aorta(73). Adult patients  
10  
11 254 with repaired coarctation of aorta have a high risk of late hypertension.

12  
13  
14 255 **Endothelial dysfunction in respiratory conditions (Table 4):**

15  
16  
17 256 4 studies used Endo-PAT in respiratory conditions (*Table 4*). Augusto et al noted an increased  
18  
19 257 augmentation index (AIx) without changes in RHI in asthmatic patients; indicating early detection of  
20  
21 258 vascular impairment may precede ED, and different mechanisms may contribute to the pathogenesis  
22  
23 259 and progression of cardiovascular events in this population(51). One study reported an improvement  
24  
25 260 in sleep disordered breathing post weight loss(52). Also, endothelial function significantly improves  
26  
27 261 after weight loss. Two studies report children with OSA compared to habitual snorers are at increased  
28  
29 262 risk for ED(53, 54). Frequent wakening due to obstructive respiratory events may be a risk factor for  
30  
31 263 ED in OSA.

32  
33  
34 264 **Endothelial dysfunction and psychological conditions (Table 5):**

35  
36  
37 265 4 studies report the use of Endo-PAT in psychiatric conditions (*Table 5*). Potential limitations in this  
38  
39 266 area are self-reported methods for detecting psychological distress of children, for example in the  
40  
41 267 LOOK longitudinal study(55). Naiberg et al (2017) utilised retinal vascular photography as a proxy  
42  
43 268 for cerebral microvasculature, and Endo-PAT to assess cardiovascular and neurocognitive burden in  
44  
45 269 adolescents with bipolar disorder (BD)(57). In the BD group, better endothelial function was  
46  
47 270 associated with higher arterio-venular ratio ( $r=0.375$ ,  $p=0.041$ ). Retinal vascular calibre was  
48  
49 271 significantly associated with endothelial function in BD and it has been suggested that it may be used  
50  
51 272 as an assessment tool in this cohort. Olive L.S. (2017) published 'The emerging field of paediatric  
52  
53 273 psycho-cardiology' highlighting the importance of the childhood origins of adult CVD(74). This  
54  
55 274 article highlights that psychological distress can influence CVD risk, directly by physiological change  
56  
57 275 that can negatively impact the integrity of the cardiovascular system.

276

**277 Endothelial dysfunction and other paediatric conditions (Table 6 – Miscellaneous)****278 *Childhood cancer survivors:***

279 There is evidence of ED in cancer survivors (*Table 6*)(60). Chemotherapy causes cardiomyocyte  
280 damage and also negatively affects endothelial function. Broberg et al (2018) utilised Endo-PAT in  
281 childhood cancer survivors and noted a lower RHI in this cohort compared to controls(75). Brouwer  
282 et al (2013) studied cancer survivor patients after potential cardiovascular toxic treatment (e.g.  
283 anthracyclines, platinum) and/or radiotherapy and noted a higher risk of ED compared with sibling  
284 controls(76). Broberg et al (2016) identified one-third of cancer survivors (31.2%) compared to 8% of  
285 controls (p= 0.02) had ED in their study(77). They concluded this may be a useful screening tool of  
286 cardiovascular disease in asymptomatic cancer survivor patients. Pao et al (2018) assessed the  
287 relationship between blood pressure and ED using Endo-PAT in haematopoietic stem cell transplant  
288 recipients. Hypertension on ambulatory blood pressure monitoring (p= 0.045) and blunted nocturnal  
289 dipping (p= 0.04) were associated with a lower Endo-PAT scores(78). Jehlicka et al (2011) used  
290 Endo-PAT and noted ALL patients had lower RHI compared to controls (1.57±0.50, 1.96±0.63;  
291 p≤0.05)(79).

**292 *Autoimmune conditions:***

293 Children with autoimmune diseases may have a high tendency to develop ED which was highlighted  
294 in a study using a novel technique(80). Atherosclerosis is an emerging cause of morbidity and  
295 mortality in patients with rheumatological conditions such as juvenile idiopathic arthritis, SLE and  
296 dermatomyositis. Borenstein-Levin et al assessed a cohort with autoimmune conditions compared to  
297 controls: 29% in the study group had ED compared to 6% (p <0.05)(80). Chang et al noted nocturnal  
298 blood pressure (BP) non-dipping is associated with ED in SLE patients highlighting a potential role  
299 for ambulatory BP monitoring in these patients(*Table 3*)(7).

**300 *Metabolic diseases:***

1  
2  
3 301 Yano et al research in Fabry disease patients demonstrated that early diagnosis of ED can help  
4  
5 302 determine the timing of initiating enzyme replacement therapy(81). Utilizing RH-PAT as a screening  
6  
7 303 tool for early renal involvement may be helpful as it may detect abnormalities even prior to  
8  
9 304 microalbuminuria(82). This can provide guidance on enzyme replacement therapy which is required  
10  
11 305 to prevent irreversible progressive renal failure. Al Jasmi et al research in mitochondrial diseases  
12  
13 306 reported that arginine or citrulline supplementation may improve ED, which provides evidence that  
14  
15 307 these amino acids may be therapeutic (*Table 6*)(62).

17  
18 308 ***Inflammatory bowel disease:***

19  
20  
21 309 One study (*Table 6*) highlights that IBD patients had lower RHI compared with controls(59). Petr et al  
22  
23 310 (2014) provided evidence of increased ED in children with Crohn's disease compared to healthy  
24  
25 311 controls(83). RHI values were significantly lower in the patients with Crohn's than controls ( $p <$   
26  
27 312 0.05).

28  
29  
30 313 ***Infectious diseases:***

31  
32  
33 314 Dirajlal-Fargo et al used Endo-PAT to assess ED in human immunodeficiency virus (HIV) patients  
34  
35 315 (*Table 6*)(66, 84). Perinatally acquired HIV patients appear to have higher levels of ED (RHI 1.34  
36  
37 316 (1.20, 1.42) compared with controls (1.52 (1.27, 1.80) ( $p < 0.01$ ))(84). The pathogenesis of severe  
38  
39 317 Plasmodium vivax malaria is poorly understood. ED and reduced nitric oxide (NO) bioavailability  
40  
41 318 characterize severe falciparum malaria. Barber et al (2016) identified that endothelial function was  
42  
43 319 impaired in proportion to disease severity. Those with severe vivax malaria, non-severe and healthy  
44  
45 320 controls median RH-PAT index 1.49, 1.73, and 1.97 respectively ( $p = 0.018$ )(85). ED in this cohort  
46  
47 321 was associated with reduced L-arginine bioavailability, which may contribute to microvascular  
48  
49 322 pathogenesis.

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55 324 **Discussion:**

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3 325 Weaknesses of the paper include the quality of the papers are limited and varied; 11 are conference  
4  
5 326 abstracts that had little information available on methods or results and have limited analysis.  
6  
7 327 Observational studies are also limited in research value. Many are case-control studies which are not  
8  
9 328 as valuable as randomised controlled trials (RCT). Only 4 studies are RCTs. The studies cannot be  
10  
11 329 compared for a meta-analysis as most are not RCT level research of high enough quality. Therefore,  
12  
13 330 the conclusions drawn from many of these studies are limited. There may be significant findings in  
14  
15 331 studies in the grey literature or in conference presentations that was not included, for example in the  
16  
17 332 studies where 25 authors did not respond to emails. Only papers from 2015 to March 2021 were  
18  
19 333 included. Papers using other methods of ED assessment such as flow-mediated dilatation are not  
20  
21 334 included. Many of the papers did not include other factors that would be important in a cardiovascular  
22  
23 335 assessment of children, for example family history, cholesterol and blood pressure parameters and  
24  
25 336 Body Mass Index (BMI) and standardised BMI (SDS) measurements. So, in many studies it cannot be  
26  
27 337 excluded that there were confounding variables affecting the ED score. Regardless, this study  
28  
29 338 indicates that there are a significant number of published paediatric papers that indicate the presence  
30  
31 339 of ED in children as young as 8 years old.  
32  
33  
34  
35 340 Strengths of the paper include a comprehensive literature search including contacting authors by email  
36  
37 341 for separate paediatric results in studies with combined adult and paediatric data. All study types were  
38  
39 342 reviewed and even the studies without results but had interesting points were included in our  
40  
41 343 discussion. Also, we do not think that this paediatric Endo-PAT review has been done before.  
42  
43  
44 344 The potential future role of Endo-PAT for paediatric patients may be an adjunct tool to in screening  
45  
46 345 for cardiovascular risk factors as well other factors such as family history, cholesterol, blood pressure.  
47  
48 346 If atherosclerosis is identified early, it can be halted in its process in certain conditions. There is huge  
49  
50 347 potential for use in diabetic patients. Lower insulin sensitivity poses a risk of diabetic nephropathy(8).  
51  
52 348 Microangiopathic renal damage increases oxygen consumption and increases resistance in the afferent  
53  
54 349 arterioles. Shah et al report T2D patients have greater vascular thickness and stiffness and worse  
55  
56 350 endothelial function compared to obese and lean children(86). This is raising concern that adolescents  
57  
58 351 with T2D are already at risk of developing early onset cardiovascular disease.  
59  
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2  
3 352 Endo-PAT has multiple benefits in obesity (*Table 2*)(6, 34, 39). Berardinelli-Seip syndrome is a rare  
4  
5 353 condition characterized by severe insulin resistance and absence of subcutaneous fat since birth or  
6  
7 354 early childhood. Lipids can deposit in muscle, liver and arterial walls; explaining its clinical  
8  
9 355 complications of diabetes, hepatic injury, hyperlipidaemia and premature atherosclerosis. Fernandes et  
10  
11 356 al (2015) reported 50% with this syndrome had ED (RHI  $0.49 \pm 0.15$ )(87). Their results support the  
12  
13 357 risk of ED in this cohort and highlights the necessity of early intervention to avoid cardiovascular  
14  
15 358 complications.

16  
17  
18 359 Turner syndrome (TS) patients have increased cardiovascular risk factors which predispose to cardiac  
19  
20 360 and cerebrovascular complications. A literature review concluded that TS have unfavourable  
21  
22 361 cardiometabolic risk factors which predispose them to adverse cardiac and cerebrovascular outcomes  
23  
24 362 in young adulthood(88). It is unclear whether this is secondary to the syndrome itself or from  
25  
26 363 modifiable risk factors such as obesity, hypertension, etc. Moreover, congenital heart disease is a  
27  
28 364 clinical feature in 30% of cases of TS patients. There is a huge emphasis on the importance of regular  
29  
30 365 screening in this cohort and also further research into whether any variables could potentially be  
31  
32 366 altered to reduce the atherosclerosis risk in adulthood. O’Gorman et al (2012) published a case-control  
33  
34 367 study on TS patients(89). This paper excluded any with structural congenital heart disease. Lower  
35  
36 368 RHI scores in TS compared with controls 1.64 (0.34) vs 2.08 (0.32) ( $P < 0.005$ ). Growth hormone may  
37  
38 369 protect endothelial function in TS patients as GH-untreated RHI 1.44 (0.26) versus GH-treated 1.86  
39  
40 370 (0.28) ( $p < 0.05$ ). There are countless other paediatric syndromes, that could benefit from ED  
41  
42 371 screening.

43  
44  
45  
46 372 Furthermore, in cardiac diseases and post-cardiac surgery Endo-PAT has been proven useful in  
47  
48 373 multiple studies (*Table 3*)(48, 73, 88). Dietz et al (2015) systematic review and metanalysis on  
49  
50 374 peripheral ED in Kawasaki disease, report coronary arterial aneurysms had higher surrogate markers  
51  
52 375 for cardiovascular disease risk(90). This may indicate these patients should be monitored for CVD in  
53  
54 376 adulthood, however significant heterogeneity was noted. Goldstein et al (2016) by using Endo-PAT  
55  
56 377 identified multiple patient and procedural factors for Fontan survivors(91). Some determinants of RHI  
57  
58 378 included prior Norwood procedure, systolic blood pressure, resting heart rate and oxygen saturation.  
59  
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3 379 Targeted intervention of modifiable risk factors may improve long-term vascular health and  
4  
5 380 functional status in Fontan survivors. Further research by Goldstein et al (2015) noted increased  
6  
7 381 arterial stiffness and decreased endothelial function are associated with lower aerobic capacity, quality  
8  
9 382 of life (QOL) and physical activity in adolescent and young adult Fontan survivors(92). ‘The  
10  
11 383 LOVE-COARCT study’ (Long-term Outcomes and Vascular Evaluation After Successful Coarctation  
12  
13 384 of the Aorta Treatment) compares vascular function in patients with coarctation of the aorta treated  
14  
15 385 with surgery, balloon dilation or stenting and endothelial function was similar among groups(93).  
16  
17  
18  
19 386 With the rising premature population, Endo-PAT may prove useful in this cohort. Harris et al (2020)  
20  
21 387 assessed cardiovascular outcomes for those born with very low birth weights (VLBW) <1500g. The  
22  
23 388 VLBW cohort (n = 229; 71% of survivors) and term-born controls (n = 100), were assessed at age 26-  
24  
25 389 30 years. The VLBW cohort had lower RHI compared to controls(94). Endo-PAT is also used in  
26  
27 390 haematological conditions. [Sivamurthy](#) et al (2009) reported lower RHI in the majority sickle cell  
28  
29 391 disease in a paediatric population (1.53 and 1.71; p value .032). RHI was not normal in children with  
30  
31 392 chronic transfusions or hydroxyurea(95).  
32  
33  
34  
35 393 Finally, many paediatric autoimmune conditions are linked with ED(7, 80). In SLE patients, ED may  
36  
37 394 occur from impaired clearance of apoptotic cells, oxidative stress, or B cell activation with different  
38  
39 395 circulating autoantibodies(71). Regular ED assessment in SLE patients has been recommended due to  
40  
41 396 risk of subclinical atherosclerosis(71). Moreover, several factors may impact microvascular function  
42  
43 397 in children, for example puberty, which is of particular interest in our paediatric review. Bhangoo et al  
44  
45 398 report improved RHI in correlation with an increase in Tanner stages and postulated that this may be  
46  
47 399 due to sex steroids(96). If Endo-PAT is used in research in adolescents, age, sex and tanner staging  
48  
49 400 must to be taken in account when reporting RHI results(68).  
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401

**402 Conclusion:**

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58 403 There are a number of papers in the paediatric literature describing ED at young ages using Endo-  
59  
60 404 PAT. However, in many cases, there has only been a single cohort study using Endo-PAT. Further

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3 405 studies are required to validate these findings. Additionally, longitudinal studies are required to  
4  
5 406 evaluate how this ED may change as the child ages and their chronic conditions changes. Further  
6  
7 407 studies are also required that will characterise more completely the cardiovascular risk profile of these  
8  
9 408 children with chronic disease. Consensus on other vascular risk markers that could be included in  
10  
11 409 future studies is ideal and if accomplished, this would facilitate meta-analyses of studies of conditions  
12  
13 410 with relatively rare conditions. Paediatricians should start to include an approach to cardiovascular  
14  
15 411 risk assessments in their assessments of young children and adolescents, including but not limited to  
16  
17 412 those with chronic diseases.  
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29 416 **Statements and declarations:**

30  
31  
32 417 **a. Authorship contributions:**

33  
34 418 All authors contributed to the initial search strategy protocol. I deLaunois performed the online  
35  
36 419 database search. J Hayden and G McDonnell separately performed a blind screen of the abstracts and  
37  
38 420 analysed the papers. G McDonnell contacted the authors of joint adult and paediatric papers to obtain  
39  
40 421 separate paediatric data. J Hayden wrote the initial manuscript which was revised by C O’Gorman.  
41  
42 422 All authors reviewed the manuscript prior to submission.  
43  
44  
45

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47

48 424 **c. Funding:** This research received no specific grant from any funding agency in the public,  
49  
50 425 commercial or not-for-profit sectors.  
51  
52

53 426 **d. Data sharing:** search technique and data analysis are available from Rayyan software and the  
54  
55 427 corresponding author.  
56  
57

58 428 **e. Competing Interest:** No competing interests to declare  
59  
60

1  
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3 429 f. Ethical approval: this was not needed as this study was a systematic review and did not involve  
4  
5 430 human participants.  
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10 432 **References:**

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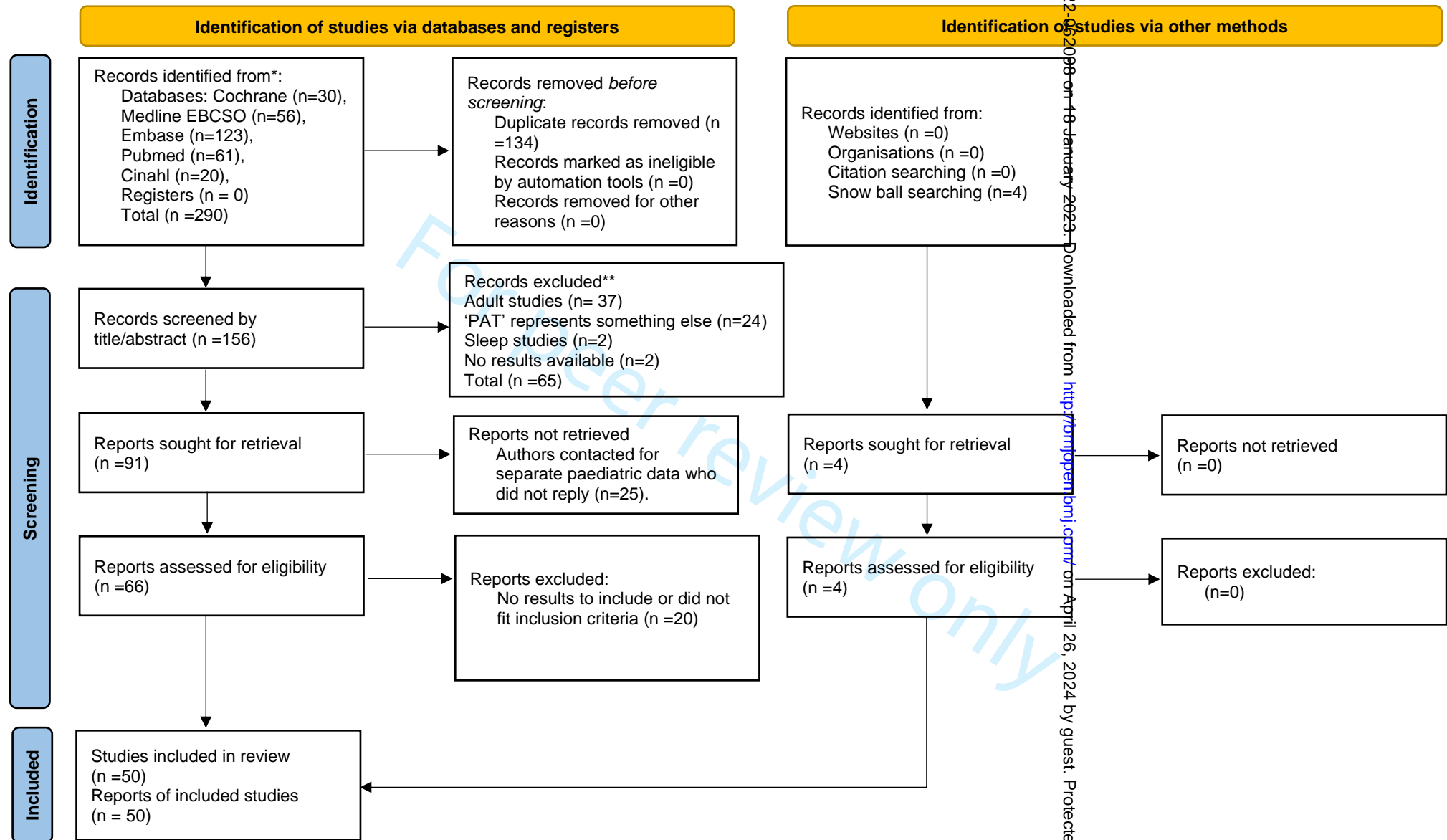
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697 Figure 1: PRISMA 2020 Flow diagram of systematic search for Endo-PAT 2000 in paediatric  
698 populations.

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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

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## PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			Page
Title	1	Identify the report as a systematic review.	2
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Tables
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analyses, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias(s)).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6



# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Flow diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Nil
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 1-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16
	23b	Discuss any limitations of the evidence included in the review.	17
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	20
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	No response
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Prospero – no response
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Nil
Competing interests	26	Declare any competing interests of review authors.	Nil
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	With authors

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# PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71  
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# BMJ Open

## Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic review.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062098.R2
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2022
Complete List of Authors:	Hayden, Jenny; RCPI O'Donnell, Gill; University Hospital Limerick, Department of Paediatrics deLaunois, Isabelle; University of Limerick O'Gorman, Clodagh; Graduate Entry Medical School, University of Limerick, Paediatrics; University Hospital Limerick,
<b>Primary Subject Heading</b>:	Paediatrics
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice, Nutrition and metabolism, Sports and exercise medicine, Medical management
Keywords:	PAEDIATRICS, Community child health < PAEDIATRICS, Paediatric endocrinology < PAEDIATRICS, EDUCATION & TRAINING (see Medical Education & Training), Change management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisational development < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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6 2 **Title page**  
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14 5 **Endo Peripheral Arterial Tonometry (Endo-PAT 2000) use in Paediatric Patients – a systematic**  
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16 6 **review.**  
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21  
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43 16  
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46 17 **Key words:** Endo-PAT 2000, peripheral artery tonometry, Endothelial dysfunction, paediatric  
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48 18 diabetes mellitus, chronic diseases  
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51 19 **Word count:**  
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3 **23 Abstract:**  
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6 **24 Objectives:** Endo Peripheral Artery Tonometry (EndoPAT-2000) is a non-invasive technology for  
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8 **25** measuring endothelial dysfunction (ED). The reactive hyperaemia index (RHI) is resulted and is low  
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10 **26** when ED is present. We aim to synthesise the literature on paediatric ED that utilised Endo-PAT  
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12 **27** analysis.  
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15 **28 Design:**  
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18 **29** A comprehensive systematic review was conducted from January 2015 to March 2021. The databases  
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20 **30** included Cochrane, MEDLINE EBSCO, EMBASE (Ovid), PUBMED and CINAHL EBSCO.  
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22 **31** Exclusion criteria were: 1. If a study used a different device for example. 2. If the study had no  
23  
24 **32** results. Inclusion criteria were: 1. Published in the English; 2. More than 50% of study subjects were  
25  
26 **33** in the paediatric age range; 3. Data relevant to paediatric age range children could be extrapolated  
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28 **34** from all data, where not all study subjects were children.  
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31 **35 Results:**  
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34 **36** Following the removal of duplicates, 156 articles were initially identified . Following exclusion, 50  
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36 **37** articles were included for review. We have subdivided these papers into different systems for ease of  
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38 **38** reference and have reported our findings in 6 tables: patients with type 1/2 diabetes, obesity,  
39  
40 **39** cardiovascular, respiratory, psychiatric conditions and miscellaneous diseases. For each, the study  
41  
42 **40** design, population, control group (if available), RHI results and conclusions were reported.  
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45 **41 Conclusions:**  
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48 **42** A number of papers using Endo-PAT for children with various chronic diseases have evidence of ED.  
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50 **43** However, in many cases, there has only been a single cohort study using Endo-PAT. Further studies  
51  
52 **44** are required to validate these findings and to help characterise the cardiovascular risk profile of  
53  
54 **45** children with chronic disease. Further studies are also required that will characterise more completely  
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56 **46** the cardiovascular risk profile of these children.  
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3 47 Consensus on other vascular risk markers that could be included in future studies is ideal and if  
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5 48 accomplished, this would facilitate meta-analyses of studies of relatively rare conditions.  
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16 52 **Strengths and limitations:**

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19 53 • Comprehensive systematic review to synthesise the literature on endothelial dysfunction  
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21 54 using Endo-PAT in paediatric patients.  
22  
23 55 • All study types were reviewed and even the studies without results but were relevant were  
24  
25 56 included in our discussion.  
26  
27  
28 57 • In many cases, there has only been a single cohort study using Endo-PAT for a particular  
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30 58 disease  
31  
32 59 • Separate paediatric results were obtained where possible from studies with combined adult  
33  
34 60 and paediatric data; however, some papers were of poor quality and had limited results  
35  
36 61 available  
37  
38 62 • Only papers from January 2015 to March 2021 were included in our review.  
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45 65 **Introduction:**

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47 66 Endothelial dysfunction (ED) is an early predictor of cardiovascular disease(1). Negative alterations  
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49 67 in endothelial physiology, also known as ED, cause the endothelium to lose its ability to promote  
50  
51 68 vasodilation, fibrinolysis and anti-aggregation(2). It is the beginning of atherosclerosis formation  
52  
53 69 which can lead to plaque progression and luminal narrowing(3). There is an imbalance between  
54  
55 70 vasodilation and vasoconstriction, abnormal reactive oxygen species, and nitric oxide (NO)  
56  
57 71 bioavailability(2). ED is a complication of cardiovascular risk factors such as smoking,  
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3 72 hypercholesterolemia, hypertension, hyperglycaemia and family history of premature atherosclerosis.  
4  
5 73 ED can be caused by oxidative stress with loss of vaso-active or inflammatory homeostasis within the  
6  
7 74 body's vascular system. It may be secondary to mechanical stimuli, for example increased  
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9 75 intraluminal pressure within the blood vessel or metabolic factors such as hormones (oestrogen's  
10  
11 76 vasodilation action)(4).

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14 77 Damaged endothelium can release a cascade of substances which pose a risk of thrombosis,  
15  
16 78 inflammation and ultimately atherosclerosis(5). ED in paediatric populations has been associated with  
17  
18 79 several conditions including type 1 diabetes (T1D), type 2 diabetes (T2D), renal impairment, obesity  
19  
20 80 and metabolic syndrome(6-9). In patients with T2D, obesity and metabolic syndrome, insulin  
21  
22 81 resistance is one of the most importance factors contributing to ED(9). Metabolic syndrome is a pro-  
23  
24 82 inflammatory state where dyslipidaemia, hyperuricemia, and hypertension occur and can predispose  
25  
26 83 to ED(10).

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29  
30 84 ED can progress to atherosclerosis which is a chronic condition that poses severe risk of certain  
31  
32 85 diseases including coronary artery disease, stroke and peripheral arterial disease. If detected early and  
33  
34 86 specific patient modifications are made, the progression to permanent vessel damage may be halted.  
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36 87 ED can be detected by invasive techniques assessing the coronary vessels or by non-invasive  
37  
38 88 techniques via the peripheral circulation. The gold standard test would utilise coronary angiography  
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40 89 and assess response to vasodilators. However, this is not feasible in practice as a screening tool,  
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42 90 especially in paediatrics.

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45 91 This review highlights the variety of conditions that Endothelial Peripheral Artery Tonometry (Endo-  
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47 92 PAT) can be useful in paediatric patients. This systematic review will add to other reviews of  
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49 93 endothelial function assessments in paediatric populations as it includes further studies and an  
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51 94 increasing variety of paediatric conditions as well(11).

#### 52 53 54 95 **Endo-PAT 2000:**

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57 96 Endo-PAT 2000 is a non-invasive technology for measuring ED developed by Itamar Ltd. Non-  
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59 97 invasive pneumatic probes which are placed on the both index fingers, which continuously records  
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3 98 pulse wave amplitude. A blood pressure cuff is inflated to occlude blood flow and response after  
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5 99 deflation is recorded. The reactive hyperaemic index (RHI) is resulted following this mini-ischemic  
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7 100 stress to the vessel. The pulse wave amplitude (PWA) is measured and computes a RHI result  
8  
9 101 automatically. RHI is calculated as the ratio of average PWA divided by the average amplitude during  
10  
11 102 the equilibration period. To compensate for any systemic changes, this ratio is normalized to a  
12  
13 103 concurrent signal from the contralateral finger.

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16 104 Numerous studies in both adult and paediatric literature reveal Endo-PAT's excellent reproducibility  
17  
18 105 and reliability(12-14). However, RHI has limitations as a reliable method for defining ED, especially  
19  
20 106 in paediatric patients due to the metabolic change's children go through throughout childhood  
21  
22 107 including growth and puberty. There is no RHI cut off value in paediatric patients. In ED, the RHI is  
23  
24 108 low and pulse amplitude is high. PAT also provides results on the peripheral augmentation index  
25  
26 109 (PAT-AIx). Bonetti et al report a RHI of <1.35-1.49 as indicative of coronary ED in adults(14, 15).

27  
28  
29 110 Prior to Endo-PAT, ED had been assessed by flow-mediated vasodilation (FMD). FMD uses an  
30  
31 111 ultrasound to assess the change in brachial artery diameter in response to increased flow after a period  
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33 112 of vascular occlusion by a blood pressure cuff and is highly dependent on nitric oxide (NO)  
34  
35 113 bioavailability. ED is identified by less vasodilatation (reduced FMD) of the brachial artery. FMD is  
36  
37 114 technically challenging to perform, user-dependent and requires training. FMD results macro blood  
38  
39 115 vessel reactivity whereas Endo-PAT results micro, which may account for the challenges in  
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41 116 comparing the two techniques. Endo-PAT is easier to set up, is automated and less user-dependent. It  
42  
43 117 can be used at the patient's bedside, without extensive training required of the operator. Wilk et al  
44  
45 118 reported that RHI correlated with FMD ( $r = 0.35$ ,  $P < 0.01$ ) however there are other studies who have  
46  
47 119 not reported a correlation between the two techniques(16).

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51 120 **Objective:**

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54 121 A systematic review was conducted on the use of Endo-PAT 2000 in paediatric populations in  
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56 122 assessing the risk of ED, with the aim of synthesising the literature, to determine a cohort of paediatric  
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58 123 patients at high risk of ED and who may benefit from screening.  
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45 **125 Methods:**  
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8 126 A comprehensive systematic review was conducted to identify publications that investigated Endo-  
9 PAT 2000. All papers published from January 2015 to March 2021 in paediatric populations age birth  
10 127 to 16 years of age were analysed. PRIMSA study design was used.  
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15 129 The following scientific databases were searched: The Cochrane Database, MEDLINE EBSCO,  
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17 130 EMBASE (Ovid), PUBMED and CINAHL EBSCO. The search was limited by to English studies.  
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19 131 The search was limited by type of subjects (human), date (2015 to March 2021) and included all study  
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21 132 types. Snowballing method was used. Authors of joint adult and paediatric papers were contacted by  
22

23 133 email to obtain separate paediatric data.  
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26 134 The database search was repeated several times using the combinations of keywords, MeSH terms and  
27

28 135 filters (child: birth-16 years). The following MeSH terms or key words were used for searching:  
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30 136 Peripheral arterial tonometry, PAT test, endopat, adolescent, ado\*, child, paediatric, pediatric,  
31

32 137 preschool, schoolboy, schoolgirl, boy, girl, teen, toddler, infant, baby.  
33  
34

35 138 Exclusion criteria were: 1. If a study used a different device for example 'Watch-PAT;' 2. If the study  
36

37 139 had no results. Inclusion criteria were: 1. Published in the English; 2. More than 50% of study  
38

39 140 subjects were in the paediatric age range; 3. Data relevant to paediatric age range children could be  
40

41 141 extrapolated from all data, where not all study subjects were children. A child was defined as up to 16  
42

43 142 years, and this is consistent with PubMed's definition of a child. Where data relevant to children  
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45 143 could not be extrapolated from the whole dataset, the study authors were contacted for additional  
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47 144 information prior to study inclusion or exclusion.  
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50 **145 Patient and public involvement:**  
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52  
53 146 No patient involved.  
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56 **147 Data collection and analysis:**  
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148 A total of 290 articles were obtained via the online database search (*Figure 1*: flow diagram).

149 Following removal of duplicates, 158 articles remained. The second screening was conducted by  
150 'Rayyan- systematic review software.' Two further duplicate articles were removed, with 156  
151 remaining for review.

152 Two independent authors separately performed a blind screen on the 156 abstracts. 65 articles were  
153 initially excluded based on title or abstract: 37 adult studies, 18 'PAT' did not represent peripheral  
154 arterial tonometry (e.g. prism adaptation test, psychosocial assessment tool), 6 Watch-PAT, 2 sleep  
155 studies and 2 had no results available.

156 The remaining 91 articles were analysed viewing full text articles for further information. A further 20  
157 were excluded as they did not fit inclusion criteria or have results to report. Some of these articles that  
158 included Endo-PAT 2000 in paediatrics did not have results for the systematic review but had  
159 conclusions that were relevant to the paper were referenced in the results section.

160 Twenty-eight authors of studies including both adults and paediatric patients were contacted twice by  
161 email to gather separate information on the paediatric participants. Twenty authors did not reply and  
162 were thus excluded. Eight authors replied: three providing results, four unable to give separate  
163 paediatric data and one author's research was on adult patients so was excluded. Three of the articles  
164 whose authors replied with data were included in our review. Four studies were obtained via snow  
165 balling searching.

166 A total of 50 articles were included in our results and are represented in tables 1-6. For each eligible  
167 study the following data was reported: author, year of publication, design of the study, population  
168 studied, control group (if available), RHI results.

Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Adolescents and young adults with	2015	Cohort prospective	n=73 T1D adolescents,	No controls.	56 (76.7%) had ED, with lower mean RHI	T1D adolescents had evidence of

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1 2 3 4 5 6 7 8 9 10 11 12 13 14	type 1 diabetes display a high prevalence of endothelial dysfunction. Scaramuzza et al (17)		observational study. Results at baseline and after a 1-year follow-up	diagnosed > 1 year, 16.2 +/- 3.5 years, [F/M 25/48]		scores (1.26 ± 0.22 versus 2.24 ± 0.48, p < 0.0001). More with ED had abnormal cardiac autonomic tests (p = 0.02) and were more sedentary. After 1 year follow-up in 64/73 patients, 81.8% had ED, despite some improvement in HbA1c.	ED. Good metabolic control (HbA1c ≤7.5%) and regular physical activity might be protective. ED progression despite some improvement to HbA1c.
15 16 17 18 19 20 21 22 23 24 25 26 27	Alpha-Lipoic Acid and Antioxidant Diet Help to Improve Endothelial Dysfunction in Adolescents with Type 1 Diabetes: A Pilot Trial. Scaramuzza et al (18)	2015	Double-blind, randomized controlled trial – snowballing. Results at baseline and after follow-up	n=71 T1D patients, followed for at least 1 year, age 16.3 ± 3.4 years, [F/M 29/42]. (a) antioxidant diet 10,000 ORAC + alpha-lipoic acid; (b) antioxidant diet 10,000 ORAC + placebo;	(c) controls	3 double-blind study arms: (a) antioxidant diet 10,000 ORAC + lipoic acid: RHI 1.40 ± 0.68 vs 1.72 ± 0.66 (P<0.05) (baseline vs after 6 months). (b) antioxidant diet 10,000 ORAC + placebo: RHI 1.39 ± 0.41 vs 1.58 ± 0.40 (P>0.05). (c) Controls: RHI 1.58 ± 0.64 vs 1.54 ± 0.42 (P>0.05).	Improved RHI with alpha-lipoic acid in T1D patients.
28 29 30 31 32 33 34 35 36 37 38 39	Effect of metformin on endothelial function in overweight adolescents with type 1 diabetes (T1D). Nadeau et al(19)	2016	Conference abstract. Endo-PAT scores at baseline and 13 weeks.	Total n=70 overweight T1D patients. n= 41 on metformin (up to 2000 mg/day), 12-19 years (mean 15.8)	n=29 placebo group.	Mean baseline RHI 1.8 +/- 0.6 in metformin group and 1.7 +/- 0.6 placebo group. At 13 weeks, no significant change from baseline RHI (+0.1 in metformin vs. -0.0 in placebo, P = 0.08). Some improvement in endothelial function in males.	No significant RHI change with metformin overall but some improvement in overweight T1D males.
40 41 42 43 44 45 46 47 48	Assessment of biomarkers of inflammation and premature atherosclerosis in adolescents with type-1 diabetes mellitus. Babar et al (20)	2019	Cross-sectional study	T1D adolescents ≥12 years. Two groups based on different HbA1c ranges. (a) HbA1c ≥9.5% (n=25)	(b) HbA1c ≤8.5% (n=27).	PAT results were not significantly different between the groups. Pearson correlation showed a significant direct relationship between rising HbA1c and PAT (p=0.03, r=0.31).	Suboptimal glycemic control (rising HbA1c) causes early atherosclerosis.
49 50 51 52 53 54 55 56	Improvements in peripheral vascular function with vitamin D treatment in deficient adolescents with type 1 diabetes. Deda et al (21)	2018	Research article – snowballing. Tested at two different time points.	n=21 T1D patients followed for ~2 years. 25-OH-Vit. D levels < 37.5 nmol/L. Age 15.7 ± 1.4 years, [F/M 19/12]	Controls: matched age, sex and T1D.	After 4.8 ± 1.3 months of Vit. D supplementation RHI improved: 1.83 ± 0.42 vs 2.02 ± 0.68 (P<0.05).	Vit. D supplementation associated with improvement to endothelial function and reduced urinary inflammatory markers.
57 58 59 60	Non-alcoholic Fatty Liver Disease in Hispanic Youth with Dysglycemia:	2017	Cross-sectional study	n=23 overweight/obese with NAFLD, age 15.2 ± 0.5 years.	n=13 overweight/obese without NAFLD, age	NAFLD group had lower RHI (1.4 ± 0.05 vs 1.7 ± 0.09, p=0.002).. Hepatic fat is	Hepatic fat and AST/ALT levels inversely related to RHI. If

Risk for Subclinical Atherosclerosis? Bacha et al (22)			n=12 prediabetes, n=11 T2D, [F/M 13/10]	15.7 ± 0.4 years. n=8 pre-diabetes, n=5 T2D, [F/M 3/10]	inversely related to RHI (r = -0.49, P = 0.002).	dysglycemia, NAFLD is associated with worse ED.
Endothelial function in youth: A Biomarker modulated by adiposity-related insulin resistance. Tomsa et al (23)	2016	Cross sectional study	Total n = 60. n=25 obese without DM, n=19 obese with impaired glucose tolerance, n=16 obese T2D but HB1Ac < 8%. Age 15.5 (0.2), [F/M 37/23]	n=21 normal weight, age 15.5 (0.2), [F/M 9/12]	RHI inversely related to % body fat (r = -0.29, P = .008), total (r = -0.37, P = .004), subcutaneous (r = -0.39, P = .003), and visceral abdominal fat (r = -0.26, P = .04).	Childhood obesity is associated with ED (lower RHI). RHI lower in obese and T2D. RHI negatively related with percentage body fat, WC, Leptin, TNF-alpha, blood glucose.
Circulating fibroblast growth factor-21 (FGF-21): A biomarker of subclinical atherosclerosis in obese youth with non-alcoholic fatty liver disease (NAFLD)? Bacha et al (24)	2017	Conference abstract	Obese adolescents with NAFLD, 15.4+/-0.3 years. n=13 normal glucose tolerance, n=19 prediabetes, n=16 T2D patients	Control group: no NAFLD. No difference in age/gender between groups.	Lower RHI in NAFLD group. High FGF-21 concentrations related to RHI (r=-0.33, p=0.03).	Increased FGF-21 in obese adolescents with NAFLD associated with insulin sensitivity and ED. FGF-21 may constitute a biomarker ED.
Assessment of Microvascular Function in Children and Adolescents with Diabetes and Obesity. Kochummen et al(25)	2019	Cross-sectional study	DM group. n=33 T1D with normal weight. n=8 obese T2D, age 12.7 (3.8) years, [F/M 25/16]	n=17 obese, non-DM children (normal BGL, BP and lipid profile), 12.8 (2.7) years, [F/M 9/8]	For every 1% increase in HbA1C, RHI decreased by 0.097 (P = 0.01). RHI of DM group with HbA1C <10% (1.70 ± 0.58) versus those with ≥10% (1.21 ± 0.19) (p= 0.02).	Poorly-controlled DM (HbA1C ≥ 10%) had lower RHI. RHI negatively related with HbA1C. RHI similar between obese and normal weight with T1D. Similar between T1D and T2D.
Free Vitamin D: Relationship to Insulin Sensitivity and Vascular Health in Youth. Bacha et al (26)	2019	Cross-sectional study. Comparison across tertiles of free 25(OH)D concentrations	n=79, age 15.4 ± 0.2 years, [F/M 45/34]. n=30 overweight. n=31 overweight with prediabetes	n=18 normal weight and normal glucose tolerance.	The lowest tertile group had lower RHI (1.42 ± 0.06, 1.54 ± 0.06, and 1.77 ± 0.09, P = 0.002), compared with the second and third tertiles.	Youth with low free 25(OH)D or BioD concentrations have lower insulin sensitivity and worse endothelial function.
Urine Albumin-to-Creatinine Ratio (UACR): A Marker of Early Endothelial Dysfunction in Youth. Bartz et al(27)	2015	Control study. Fasting UACR analysed.	n=25 overweight (OW) with normal glucose tolerance, 15.6 ± 0.2 years, [F/M 17/8]. n=20 OWwith prediabetes, [F/M 11/9].	n=13 normal weight, 16.3 ± 0.4, [F/M 7/6].	Normal weight group RHI 1.84 ± 0.1. OW with normal glucose tolerance 1.56 ± 0.1. OW with prediabetes 1.56 ± 0.1 (P = .04). UACR was related to RHI (r = -0.33, p = .01).	UACR is an early marker of endothelial dysfunction in youth, independent of glycemia.

170 Table 1: Total of 11 studies included. Endo-PAT 2000 in paediatric type 1 diabetes mellitus (T1D) patients (5

171 studies), type 2 diabetes and prediabetes (6 studies). Reactive hyperemia index (RHI), type 1 diabetes mellitus

172 (T1D), type 2 diabetes mellitus (T2D), endothelial dysfunction (ED), Oxygen radical absorbance capacity units  
 173 (ORAC), non-alcoholic fatty liver disease (NAFLD), overweight (OW), Urine Albumin-to-Creatinine Ratio  
 174 (UACR).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Effects of a dietary strawberry powder on parameters of vascular health in adolescent males. Djurica et al (28)	2016	Randomised, double-blind, cross-over study	n=15 OW/obese males, 14-18 years (mean 16). 1-week daily 50g freeze-dried strawberry powder (FDSP) Before/after nitrate/nitrite levels measured.	n=10 control powder, 14-18 years (mean 16).	Acute plasma nitrate/nitrite levels increased 1 h after consuming the FDSP (P<0.001). When nitrate levels increased after FDSP intake compared to controls, had an increase in RHI (P=0.014).	Strawberries can provide vascular health benefits to OW/obese adolescent males.
Flow-mediated dilation in obese adolescents: Correlation with waist circumference (WC) and systolic blood pressure (SBP). Hussid et al (29)	2018	Case control study	n=20 obese patients, median age 14 years	n=10 normal weight, median age 15 years, paired for gender	No RHI difference between groups. 35% obese group had metabolic syndrome, none in control group. OSA in 86.6% obese and 50% of normal weight group.	Obese group had evidence of ED and metabolic syndrome. Increased WC and SBP seem to be related to this finding.
Improvement of microvascular endothelial dysfunction induced by exercise and diet is associated with microRNA-126 in obese adolescents. Donghui et al (30)	2019	Quasi-randomized study	n=57 obese male adolescents, 12-18 (15.38 $\pm$ 2.82) years, [F/M = 0/57], 6-week exercise program with dietary intervention.	n=10 normal weight adolescents, 15.38 $\pm$ 2.82 years, [F/M 0/10], maintained sedentary	Obese group RHI 1.43 (0.35) vs controls 1.67 (0.36) (p< 0.05). After 6 weeks RHI increased (p <0.01) and microRNA-126 decreased (p<0.01). miRNA-126 positively correlated with $\Delta$ RHI (r = 0.69, p<0.05).	RHI improved in obese group after exercise and diet interventions. Findings might be related to changes in serum miRNA-126.
Distribution of peripheral arterial stiffness and endothelial function as well as their correlations with cardiovascular risk factors in children and adolescents. Mu et al (31)	2016	Cross-sectional population-based study, conference abstract	n=94 obese, 7-17 years, used automatic waveform analyser (BP-203RPE-I) and Endo-PAT 2000.	n=452 normal-weight	In normal weight group, RHI increased with age (r=0.33, P<0.01; r=0.36, P<0.01). RHI positively correlated with BMI (r=0.10, P=0.018) but negatively with DBP (r=-0.10, P= 0.016).	RHI increased along with age. Arterial stiffness and endothelial function continued to develop in the normal weight group.
Urinary biomarkers as indicator of chronic inflammation and	2017	Control study, research	n=63 total. n=14 overweight (OW), n=29 obese, age	n=20 normal weight (NW), age 13.9 (2),	There were no differences in RHI levels: NW 1.6 (0.1),	No significant correlation between RHI

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endothelial dysfunction in obese adolescents. Singh et al(32)		article	13.8 (2.4), [F/M 23/20]	[F/M 8/12]	OW 1.66 (0.1) and obese 1.67(0.1). NW girls RHI 1.9 vs NW boys 1.25.	and urinary markers. RHI higher in NW female adolescents.
Prevalence of Type D personality in obese adolescents and associated cardiovascular risk. Bruyndonckx et al(33)	2018	Control study, conference abstract	Obese adolescents- no definite numbers	Healthy normal weight children	Positive correlation in obese adolescents between negative affectivity and vascular stiffness (r= 0.28; p= .04)	Obese adolescents have worse cardiovascular risk profile with ED.
Endothelial function and arterial stiffness in obese adolescents - A relation to baroreflex function. Czipelova et al(34)	2017	Conference abstract	n=22 obese, 15.28 +/- 2.8 years, [F/M 10/12]	n=22 non-obese, 15.98 +/- 2.46 years, [F/M 10/12]	No significant difference in RHI (p = 0.473). Baro-reflex sensitivity was also calculated.	No difference in RHI between groups. Findings require further study.
Obesity in children and adolescents: A relation to endothelial function and arterial stiffness. Czipelova et al(35)	2016	Conference abstract	n=16 obese adolescents, 15.22 +/- 2.2 years, [F/M 7/9]	n=16 non-obese, 16.22 +/- 1.5 years, [F/M 7/9]	Significant difference in RHI (p = 0.018) with RHI higher in obese group (1.66 +/- 0.28 vrs 1.4 +/- 0.25).	Less early atherosclerotic changes in obese group; in contrast to expectations. Findings require further study.
Preclinical vascular alterations in obese adolescents detected by Laser-Doppler Flowmetry technique. Fusco et al (36)	2020	Research article	n=22 obese adolescents, 14.11 +/-2.53, [F/M 13/9]	n=24 normal-weight, 15.2 +/- 1.56, [F/M 11/13]	Similar RHI between obese and non-obese groups (1.80 +/- 0.62 and 1.86 +/- 0.51).	RHI did not differ between groups. RHI did not correlate with LDF.
Impaired endothelial function in adolescents with overweight or obesity measured by peripheral artery tonometry. Pareyn et al (37)	2015	Cross sectional study	n=27 overweight (OW)/obesity, 14.7 (13.0–16.4) years, [F/M 11/16]	n=25 normal weight controls, 15.5 (13.9–16.2) years, [F/M 13/12]	RHI normal weight 1.88 (1.7-2.4) vs OW/obese 1.5 (1.3-1.9) (p< 0.05). Lower RHI if OW/obese (p = 0.027). RHI positively correlated with age and tanner stage (P< 0.05).	ED and higher baseline pulse amplitude in OW group.
C-type natriuretic peptide (CNP) plasma levels and whole blood mRNA expression show different trends in adolescents with different degree of endothelial dysfunction. Del Ry et al(38)	2020	Research article - snow balling	n=16 primary obesity, not DM, age 13.3 (0.5) years, [F/M 8/8].	n=24 normal weight, age 14.3 (0.4) years, [F/M 14/10].	RHI normal weight 2.1 (0) vs obese 1.4 (0) (P< 0.005). RHI negatively associated with CNP and diastolic BP (P< 0.005).	RHI significantly lower in obese group. RHI negatively related with CNP, DBP, fat mass and HbA1C.
C-type natriuretic peptide (CNP) is closely associated to obesity in Caucasian adolescents. Del Ry et al (39)	2016	Research article - snow balling	n=10 overweight, age 12.8 (1.6) years, [F/M 5/5]. n=45 obese, 12.8 (1.6) years, [F/M 19/26]	n=27 normal weight, age 12.8 (1.4) years, [F/M 14/13]	Normal weight group RHI 2.1 (0.2) vs OW 1.6 (0.4) (P< 0.05). Normal weight vs obese group RHI 1.4 (0.3) (P< 0.005). RHI negatively associated with CNP (P< 0.005).	RHI lower in overweight/ obese groups. CNP negatively related with RHI.
Arterial Stiffness and Endothelial Function in Young Obese Patients -	2019	Research article	Author contacted for separate paediatric data.	n=15 controls, age <16 years, [F/M 7/8]	RHI control vrs obese groups: 1.320 ± 0.427 and 1.457 ± 0.280. RHI	RHI is influenced by vascular tone

Vascular Resistance Matters. Czippelova et al (7)			n=16 obese group, age <16 years, [F/M 7/9]		obese girls and boys: 1.410 ± 0.253 and 1.494 ± 0.308. RHI control girls and boys: 1.171 ± 0.210 and 1.436 ± 0.524	and resistance. RHI in obese positively related with SVR.
Cardiovascular adaptations after 10 months of intense school-based physical training for 8- to 10-year-old children. Larsen et al (40)	2018	Randomised control study	n=93 small-sided games group, 9.3±/0.4 years. n=83 circuit strength training group, 9.3±/0.3 years (10-16 years)	n = 115 controls, 9.3±/0.3 years	No significant differences in RHI. Pubertal status is a main predictor of RHI; positive correlation between Tanner stages and RHI.	10 months of regular exercise per week decreased DBP and had effects on cardiovascular health.

177 Table 2: Endo-PAT 2000 in paediatric patients who are overweight (OW)/obese (14 studies). Reactive

178 hyperemia index (RHI), freeze-dried strawberry powder (FDSP), endothelial dysfunction (ED), overweight

179 (OW), normal weight (NW), waist circumference (WC), C-type natriuretic peptide (CNP), Laser-Doppler

180 Flowmetry (LDF).

Title, lead author	Year	Study design	Population: n=sample size, age; mean ± SD or median (range), [F/M]	Control group: n=sample size, age; mean ± SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Nocturnal blood pressure dipping as a marker of endothelial and cardiac function in pediatric-onset systemic lupus erythematosus (SLE). Chang et al (8)	2020	Cross-sectional study – author contacted for separate paed data	n=20, 9-19 years (mean 16.5), (7 were age 16 or under). Average disease duration 3.2 years (± 2.1). [F/M 17/3]	Separated into 2 groups based on nocturnal BP dipping status.	Mean RHI for n=7 (aged 16/under): 0.529. 22% had ED. Reduced diastolic BP dipping was associated with poorer endothelial function (r 0.5, p=0.04).	Isolated nocturnal BP non-dipping is associated with ED and atherosclerotic changes. Potential role for routine ABPM for youth with SLE.
Physiological changes in blood pressure (BP) impact peripheral endothelial function during adolescence. Deda et al (41)	2015	Control study. Assessing association between RHI and known cardiovascular risk factors.	n =90 healthy adolescents to assess normal RHI response, 14.2±1.91 years, [F/M 46/44].	No controls	Mean arterial pressure significantly associated with RHI (p=0.01). Positive correlation RHI and age in females (r=0.33, p<0.02). RHI correlated with pubertal status: males (r=0.411, p=0.03), females (r=0.36, p=0.03).	Physiological changes in BP significantly impact RHI results.
Endothelial Function and Arterial Stiffness Relate to Functional Outcomes in Adolescent and Young Adult	2016	Cross-sectional prospective observational study	n=60, 8-25 years (mean 13.9±4.1), [F/M 29/31]	No controls	PAT derived baseline pulse amplitude (P<0.05) negatively associated with minute ventilation to CO2 ratio. RHI 1.2 (0.2–4.8).	Worse vascular measures associated with worse functional measures. Increased arterial stiffness and decreased endothelial function are associated with lower

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Fontan Survivors. Goldstein et al (42)						aerobic capacity, physical activity, and QOL in Fontan survivors.
Natural history of vascular function in adolescent and young adult Fontan survivors: A longitudinal assessment of endothelial function and arterial stiffness. Goldstein et al (43)	2017	Prospective single-centre longitudinal study, conference abstract. Paired testing at a mean interval of 2.0 +/- 0.2 years of Fontan survivors.	n=50, mean 13.7 +/- 4.2 years, [F/M 23/27]	No controls	Decreases in RHI (0.002 +/- 0.01/yr) were not significant. BMI was a predictor for RHI (R 0.17, p=0.007).	Vascular function does not change uniformly in Fontan survivors. Changes in vascular function do not relate to changes in aerobic capacity but are associated with changes in anthropometric measures and O2 saturation.
Vascular function long term after Kawasaki disease: another piece of the puzzle? Pinto et al (44)	2017	Single-centre prospective study	n=43 Kawasaki patients, age >11 years, diagnosed >5 years ago, with no coronary lesions or any other risk factors for cardiovascular disease.	n= 43 control group of individuals without cardiovascular risk factors.	Kawasaki patients had decreased RHI compared with controls (1.59±0.45 versus 1.98±0.41; p<0.001).	Children with Kawasaki disease may have long-term sequelae, even when there is no detectable coronary artery involvement in the acute stage of disease.
Endothelial function in children with a history of Henoch Schonlein purpura (HSP). Butbul Aviel et al (45)	2017	Observational prospective study	n=19 with HSP, 13.5 ± 3.9 years, [F/M 8/11]	n=23 healthy children, 12.8 ± 4.5 years, [F/M 7/16]	Mean RHI 1.81 study group and 1.87 control group (p = 0.18). RHI higher in patients who had endothelial function measured >6 years since HSP diagnosis compared with <6 years (1.98 + 0.74 vs. 1.38 ± 0.43 P = 0.037).	This study suggests that HSP causes short term endothelial dysfunction that improves with time.
Reactive hyperaemia index and detection of endothelial dysfunction in children with familial hypercholesterolaemia (FH). Jehlicka et al(46)	2015	Conference abstract	n=24 with FH, 13.9+/-2 years. Biochemical markers of endothelial function were assessed.	n=17 healthy controls, 15.2+/- 2.2 years	Significantly lower RHI in FH group (1.63+/-0.50 and 2.03+/-0.54; p<0.05). Lower RHI and elevated E-selectin in children with FH.	Possible relationship of ED in children with FH, highlighting the importance of early detection of ED when the atherosclerotic process is still reversible.

182 Table 3: Endo-PAT 2000 in paediatric patients with cardiac and vascular conditions (7 studies). Reactive

183 hyperemia index (RHI), waist circumference (WC), systolic blood pressure (BP),, peak VO (peak O2

184 consumption), quality of life (QOL), systemic lupus erythematosus (SLE), ambulatory blood pressure

185 monitoring (ABPM), quality of life (QOL), Henoch Schonlein purpura (HSP), familial hypercholesterolaemia

186 (FH).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Vascular function in asthmatic children and adolescents. Augusto et al (47)	2017	Cross-sectional controlled study	n=19 asthmatic patients, age $13.6 \pm 0.6$ years. [F/M 0/19]	n=18 controls. $14.9 \pm 0.7$ years. [F/M 0/18]	RHI were similar between groups ( $p = 0.23$ ). Asthmatic group RHI did not correlate with the different variables.	The increased AIx@75 without changes in RHI in asthmatic patients could mean that an early detection of vascular impairment may precede ED.
The effect of weight loss on endothelial function and sleep disordered breathing (SDB) in obese children. Ysebaert et al (48)	2018	Conference abstract. Baseline and reassessed after 6-month weight loss programme.	n=62 obese, age 11-19 (mean 15.8) years, [F/M 20/42]	No controls.	Baseline: 39% had SDB. After 6 months: 86% had resolution of earlier diagnosed SDB. All had significant improvement of endothelial function after programme ( $p < 0.001$ ). No correlations between SDB and improvement in endothelial function found.	Endothelial function significantly improves after weight loss.
Polysomnographic correlates of endothelial function in children with obstructive sleep apnoea (OSA). Zhang et al (49)	2018	Cross sectional study	n=121 mild OSA, $6.2 \pm 1.6$ years, [F/M 37/84]. n=127 moderate-severe OSA, $6.0 \pm 1.6$ years, [F/M 31/96]	n=107 primary snorers (PS), age $6.4 \pm 1.8$ years, [F/M 37/70]	OSA groups lower RHI than PS ( $P < 0.001$ , $P = 0.001$ ). RHI positively correlated with age ( $r = 0.17$ , $P = 0.002$ ), BMI z score ( $r = 0.14$ , $P = 0.008$ ) and oxygen saturation ( $r = 0.15$ , $P = 0.006$ ).	Children with OSA are at increased risk for abnormal endothelial function than habitually snoring children.
Endothelial dysfunction in children with obstructive sleep apnoea syndrome (OSAS). Xu et al(50)	2020	Cross sectional study	n=248 OSAS, age 3-11 years	n=107 primary snorers (PS). No significant differences in age/gender.	OSAS had lower RHI $1.1 \pm 0.1$ vs $1.2 \pm 0.2$ ( $P < 0.01$ ). RHI independently correlated with age, gender, obstructive apnoea hypopnea index, oxygen desaturation index ( $P < 0.01$ ).	OSAS have significant ED compared with PS. Frequent arousals due to obstructive respiratory events during sleep may be a candidate risk factor for ED.

188 Table 4: Endo-PAT 2000 in paediatric patients with respiratory conditions (4 studies). Endothelial dysfunction

189 (ED), reactive hyperaemia index (RHI), heart rate-corrected augmentation index (AIx@75), primary snorers

190 (PS), obstructive sleep apnoea (OSA), obstructive sleep apnoea syndrome (OSAS).

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Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
Do self-reported stress and depressive symptoms effect endothelial function in healthy youth? The LOOK longitudinal study. Olive et al(51)	2018	Longitudinal cohort study. LOOK longitudinal study, who were followed through to adolescence (16 years).	n=203, 7.6 $\pm$ 0.3 years, [F/M 111/92].	No controls.	All relationships occurred in the hypothesised direction, but no cross-sectional or prospective evidence of early psychological stress or depression was associated with ED (all p > 0.05).	Contrast to previous findings in adolescents, little evidence between current or previous psychosocial stress or depression and endothelial function in 16-year-old adolescents.
Cerebrovascular reactivity is associated with peripheral endothelial function (EF) among adolescents. Urback et al(52)	2016	Conference abstract	n=11 with bipolar disorder. EF measured by PAT and cerebrovascular reactivity (CVR) by blood-oxygen-level dependent fMRI.	n=35 healthy controls	EF was positively correlated with CVR in grey matter ( $r=0.41$ , $p=0.012$ ), and a peak voxel in the left-medial-frontal gyrus ( $r=0.35$ , $p=0.036$ ).	Breath-hold CVR and peripheral EF are linked, suggesting that vascular function may be a multi-systemic phenotype. EF may be a potential proxy for cerebral blood vessel function with greater accessibility and lower cost than fMRI.
Retinal-vascular photography as a window into the cardiovascular and neurocognitive burden of adolescent bipolar disorder (BD). Naiberg et al (53)	2017	Cross-sectional study, author emailed for separate paed data-most were teenagers	n=30 with bipolar disorder, 17.97 $\pm$ 1.86 years	n=32 healthy controls, 16.00 $\pm$ 1.62 years	In BD group, higher endothelial function associated with higher arterio-venular ratio ( $r=0.375$ , $p=0.041$ ).	Retinal photography may help assessing cardiovascular and neurocognitive burden of BD.
Impact of psychological health on peripheral endothelial function and the HPA-axis activity in healthy adolescents. Chen et al(54)	2017	Longitudinal 3-year follow-up study. Baseline and three-year follow-up.	n=162, 14.5 $\pm$ 1 years. [F/M 94/68].	No controls.	Lower peripheral endothelial function was associated with high level of anger ( $\beta = -0.332$ , $p = 0.018$ ) and disruptive behaviour ( $\beta = -0.390$ , $p = 0.006$ ) over three years in males, but not in females, adjusted for covariates.	High amounts of negative emotions may have adverse effects on peripheral endothelial function and regulation of the HPA-axis activity. High level of self-concept might be protective.

196 Table 5: Endo-PAT 2000 in paediatric patients with psychiatric conditions (4 studies). Endothelial dysfunction  
 197 (ED), endothelial function (EF), cerebrovascular reactivity (CVR), bipolar disorder (BD), functional magnetic  
 198 resonance imaging (fMRI), hypothalamic-pituitary-adrenal HPA.

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	Title, lead author	Year	Study design	Population: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Control group: n=sample size, age; mean $\pm$ SD or median (range), [F/M]	Results: RHI reported. If RHI not specified, we reported p/r values	Outcomes
1 2 3 4 5 6 7 8 9 10 11	Vascular endothelial function in inflammatory bowel disease (IBD). Winderman et al (55)	2018	Case-control study	n=16 with IBD (all in clinical remission), age 16.7 $\pm$ 2.6 years, [F/M 8/7]	n=16, age 15.1 $\pm$ 2.8 years, [F/M 7/8]	RHI IBD vs controls 1.66 vs 2.02 (P =0.036). IBD group had a mean RHI within the range associated with VD risk in adults (1.67).	IBD group lower RHI compared with controls. IBD patients may need to be monitored for thromboembolic phenomena.
12 13 14 15 16 17 18 19	Endothelial health in childhood acute lymphoid leukaemia (ALL) survivors: pilot evaluation with peripheral artery tonometry. Ruble et al (56)	2015	Case control study	n=16 ALL survivors, age 8-20 years (12.9 $\pm$ 0.9), [F/M 8/8].	n=16 healthy sibling pairs 13.8 (0.9), [F/M 10/6].	Both groups similar in cardiovascular risk measures but survivors had lower RHI (1.54 vs. sibling 1.77; P=0.0474).	Evidence of poorer vascular health in cancer survivors.
20 21 22 23 24 25 26 27 28 29 30 31	Microvascular endothelial function in Japanese early adolescents. Odanaka et al (57)	2017	Control study	n=157 healthy adolescents divided by gender. Females n=82, median age 14 (1), 13.7 $\pm$ 0.9 years	Males n= 75, median age 14 (2) years	No difference in RHI according to sex: boys and girls 1.85 $\pm$ 0.6, 1.82 $\pm$ 0.66 and 1.87 $\pm$ 0.54. RHI was significantly associated with systolic and diastolic BP, and had no correlation with anthropometric parameters and arterial stiffness markers.	RHI among adolescents were similar to those reported in previous studies on children and early adolescents.
32 33 34 35 36 37 38 39 40 41	Endothelial Dysfunction and the Effect of Arginine and Citrulline Supplementation in Children and Adolescents With Mitochondrial Diseases. Al Jasmi, et al (58)	2020	Case control study	9 participants, age 6-17 years (mean 9.6).	3-15 years (mean 9.4). Baseline endothelial dysfunction was assessed in controls.	Lower RHI with mitochondrial diseases. RHI increased with arginine or citrulline supplementation	Supplementation with NO precursors may improve ED by enhancing NO production. First study to use Endo-PAT methodology in mitochondrial diseases.
42 43 44 45 46 47 48 49 50 51 52 53	Assessment of traditional and non-traditional risk factors for premature atherosclerosis in children with juvenile dermatomyositis (JDM) and pediatric controls. Wahezi et al (59)	2020	Retrospective controlled study	n=40 JDM, age 6-22 (mean 12.4 $\pm$ 4.1) years, [F/M 28/12]	n=20 controls, age 12.7 $\pm$ 3.9 years, [F/M 14/8]	RHI controls 1.43 [1.2, 1.7] and JDM 1.57 [1.2,1.9]. If controlled for lipoprotein A (atherogenic confounder), JDM patients had 41% RHI increase, thus indicating less ED compared to controls.	Rheumatological childhood disorders may be at increased risk of developing ED, but sociodemographic factors may have a greater role in developing cardiovascular disease.
54 55 56	Vascular Health of Children Conceived via	2019	Cross-sectional pilot study	n=17 IVF children, 10-14 years. Also used	Compared to published norms or to	Mean Endo-PAT index in the IVF cohort was 1.66 $\pm$ 0.52, 71% had	Children conceived by IVF seem to have evidence of abnormal

In Vitro Fertilization (IVF). Zhang et al (60)			carotid ultrasound and pulse wave velocity measurements.	historical Stanford controls	abnormal values (<1.9). Mean RHI was not significantly different between IVF and controls.	vascular health.
Endothelial dysfunction in South African youth living with perinatally acquired human immunodeficiency virus (PHIV) on antiretroviral therapy. Mahtab et al (61)	2020	Case control study	n= 431 PHIV, median 14.1 (12.8, 15.5) years, [F/M 213/218]	n=93 without HIV, median 13.9 (12.1, 15.3) years, [F/M 53/40]	PHIV had higher rates of ED (50% vs 34%; P = .01); relationship persisted after adjusting for age, sex, BMI, high BP, high cholesterol (RR, 1.43; P =0.02). PHIV, CD4 count, viral load and current ART class were not associated with ED after adjustment.	PHIV appear to have increased risk of ED. These findings have important implications as HIV has increased risk of premature CVD and complications.
Soluble CD14 (sCD14) is associated with endothelial dysfunction in South African youth on ART. Dirajlal-Fargo et al (62)	2020	Case control study	n=283 perinatally acquired HIV (PHIV), 9-14 years.	n=69 age-matched without HIV	PHIVs had lower RHI despite viral suppression (RHI=1.36 vs 1.52, p<0.01). sCD14 at 24 months correlated with ED (p<0.04). PHIV with ED, sCD14 was associated with lower RHI ( $\beta$ -0.05, p=0.01).	Higher sCD14 is independently associated with ED in PHIVs.
Role of insulin resistance and hyperandrogenemia in early vascular dysfunction in adolescents with PCOS. Bartz et al (63)	2015	Conference abstract	n=14 PCOS adolescents PCOS (on no treatment).	n=7 non-PCOS. Both groups had similar age, tanner stage, race, glucose tolerance status.	Despite higher peripheral and hepatic insulin resistance with PCOS, RHI is not significantly lower when compared with controls of similar total body and abdominal adiposity.	PCOS has evidence of increased vascular inflammation. Hyperandrogenemia and insulin resistance may play an important role in vascular inflammation.
Endothelial Function in Children and Adolescents Is Mainly Influenced by Age, Sex and Physical Activity- An Analysis of Reactive Hyperemic Peripheral Artery Tonometry. Mueller et al (64)	2017	Randomised controlled study, Leipzig School Project followed over 5-year period.	n=931 RHI measurements in 445 students, age 10-17 years (baseline 11.66±0.93). n=247: 60 minutes physical exercise (PE) daily (intervention group).	n=181: 2 units of 45 minutes PE weekly (control group).	Higher RHI in the intervention group: 0.09 [-0.05, 0.23]. Increase RHI from 1.53±0.42 in the youngest to 1.96±0.59 in the oldest students. This increase adjusted by age and sex was estimated as 0.11 [0.08, 0.14] per year.	If Endo-PAT is used for research in adolescents, age and sex must to be taken in account when reporting RHI results.

201 Table 6: Endo-PAT 2000 in paediatric patients with other miscellaneous paediatric conditions (10 studies).

202 Reactive hyperemia index (RHI), endothelial dysfunction (ED), inflammatory bowel disease (IBD), acute

203 lymphoid leukaemia (ALL), nitric oxide (NO), perinatally acquired human immunodeficiency virus (PHIV),

204 In Vitro Fertilization (IVF), soluble CD 14 (sCD14), polycystic ovarian syndrome (PCOS), physical exercise

205 (PE).

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**Results:****Endothelial dysfunction in paediatric diabetes mellitus patients (Table 1):**

Five studies involve only type 1 diabetes (T1D) patients (*Table 1*). 2/5 studies reported lower RHI results in the T1D group(17, 20). One study which included only adolescent patients, reported RHI negatively correlates with impaired metabolic control and subclinical signs of autonomic neuropathy(17). They concluded that good metabolic control ( $HbA1c \leq 7.5\%$ ) and regular physical activity might be protective against ED. One study reports an improved RHI result with an alpha-lipoic acid and antioxidant diet(18). Nadeau et al reported no significant RHI change with metformin overall but some improvement in overweight T1D males(19). Barber et al report suboptimal glycaemic control causes early atherosclerosis(20). One study noted an improvement in RHI post vitamin D supplementation in T1D patients with vitamin D deficiency(21).

6 studies focused on type 2 diabetes (T2D) and impaired glucose tolerance or 'prediabetes.' Tomsa et al note a link between insulin resistance and obesity by utilising Endo-PAT(23). They also noted that RHI is higher if HbA1c is less than 5.5%(23). Two studies compare on Non-alcoholic fatty liver disease (NAFLD), T2D and prediabetes patients(22, 24). If dysglycemia, NAFLD is associated with worse endothelial function. Circulating FGF-21 levels are elevated in obese youth with NAFLD and are associated ED and therefore may be a biomarker for ED(24). Bartz et al report urine albumin creatinine ratio (UACR) may be an early marker of ED independent of glycemia(27). Endothelial dysfunction may mediate the link between obesity-related insulin resistance and early microalbuminuria.(27). Kochummen *et al* reported a mean RHI in obese adolescents without diabetes was similar to T1D and T2D patients(25). One study noted an improvement in RHI post vitamin D supplementation in T1D patients with vitamin D deficiency(21). Another study noted lower vitamin D concentrations are associated with lower insulin sensitivity and worse endothelial function (26).

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**Endothelial dysfunction and Obesity (Table 2):**

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3 232 14 studies describe the use of Endo-PAT 2000 in overweight or obese patients (*Table 2*). Studies  
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5 233 included measurement of the following parameters: BMI, T1D, T2D, gender, pubertal stage, age,  
6  
7 234 blood pressure values, non-alcoholic fatty liver disease, obstructive sleep apnoea (OSA), insulin,  
8  
9 235 plasma glucose levels, inflammatory markers (urinary markers, CNP, micro-RNA-126, E-Selectin). In  
10  
11 236 numerous studies, RHI was significantly lower in obese groups (7, 25, 28-31, 38, 39, 65). ED may  
12  
13 237 mediate the link between obesity-related insulin resistance and early microalbuminuria(27). Exercise  
14  
15 238 and diet control improves glycolipid metabolism(40). Two studies by Czipelova et al did not find a  
16  
17 239 lower RHI in obese groups, but recommended further studies(34, 35). Noma et al (2017) report the  
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19 240 beneficial effects of exercise in paediatric patients and is an important message in reducing future  
20  
21 241 endothelial complications(66). Fusco et al noted pre-clinical microvascular changes in obese patients  
22  
23 242 compared to controls using LDF but noted no RHI change(36).

### 24 243 **Endothelial dysfunction in cardiac and vascular conditions (Table 3):**

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29 244 7 studies report the use of Endo-PAT and cardiovascular conditions (*Table 3*). Lower RHI is seen  
30  
31 245 with patients with familial hypercholesterolaemia(46). Studies assess ED in patients with systemic  
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33 246 lupus erythematosus (SLE) and Henoch Schonlein purpura (HSP)(8, 45, 67). Negishi et al (2016) used  
34  
35 247 Endo-PAT to compare Fontan survivors and healthy controls. The Fontan patients were aged 15 to 32  
36  
37 248 years. Mean RHI 0.56+ /- 0.26 in Fontan patients and 0.78+ /- 0.31 in controls (p= 0.09). RHI in  
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39 249 Fontan patients was associated with diastolic blood pressure, heart rate and haemoglobin A1c  
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41 250 level(68). Endothelial function in Fontan patients was associated with abnormal glucose tolerance and  
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43 251 arterial stiffness and therefore concluded that glucose regulation might be a potential target to  
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45 252 improve ED in this cohort. Nozaki et al (2018) assessed ED in conduit and resistance arteries and  
46  
47 253 used FMD and Endo-PAT in paediatric patients with repaired coarctation of aorta(69).

### 48 254 **Endothelial dysfunction in respiratory conditions (Table 4):**

49  
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51  
52 255 4 studies used Endo-PAT in respiratory conditions (*Table 4*). Augusto et al noted an increased  
53  
54 256 augmentation index (AIx) without changes in RHI in asthmatic patients (47). One study reported an  
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56 257 improvement in sleep disordered breathing post weight loss and also, endothelial function  
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3 258 significantly improved after weight loss(48). Two studies report children with OSA compared to  
4  
5 259 habitual snorers are at increased risk for ED(49, 50). Frequent wakening due to obstructive respiratory  
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7 260 events may be a risk factor for ED in OSA.  
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10 261 **Endothelial dysfunction and psychological conditions (Table 5):**  
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12  
13 262 4 studies report the use of Endo-PAT in psychiatric conditions (*Table 5*). Potential limitations in this  
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15 263 area are self-reported methods for detecting psychological distress of children, for example in the  
16  
17 264 LOOK longitudinal study(51). Naiberg et al (2017) utilised retinal vascular photography as a proxy  
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19 265 for cerebral microvasculature, and Endo-PAT to assess cardiovascular and neurocognitive burden in  
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21 266 adolescents with bipolar disorder (BD)(53). In the BD group, better endothelial function was  
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23 267 associated with higher arterio-venular ratio ( $r=0.375$ ,  $p=0.041$ ). Olive L.S. (2017) published ‘The  
24  
25 268 emerging field of paediatric psycho-cardiology’ highlighting the importance of the childhood origins  
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27 269 of adult CVD(70). This article highlights that psychological distress can influence CVD risk, directly  
28  
29 270 by physiological change that can negatively impact the integrity of the cardiovascular system.  
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35 272 **Endothelial dysfunction and other paediatric conditions (Table 6 – Miscellaneous)**  
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38 273 ***Childhood cancer survivors:***  
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41 274 There is evidence of ED in cancer survivors (*Table 6*)(56). Chemotherapy causes cardiomyocyte  
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43 275 damage and also negatively affects endothelial function. Broberg et al (2018) utilised Endo-PAT in  
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45 276 childhood cancer survivors and noted a lower RHI in this cohort compared to controls(71). Broberg et  
46  
47 277 al (2016) identified one-third of cancer survivors (31.2%) compared to 8% of controls ( $p= 0.02$ ) had  
48  
49 278 ED in their study(72). They concluded this may be a useful screening tool of cardiovascular disease in  
50  
51 279 asymptomatic cancer survivor patients. Pao et al (2018) assessed the relationship between blood  
52  
53 280 pressure and ED using Endo-PAT in haematopoietic stem cell transplant recipients. Hypertension on  
54  
55 281 ambulatory blood pressure monitoring ( $p= 0.045$ ) and blunted nocturnal dipping ( $p= 0.04$ ) were  
56  
57 282 associated with a lower Endo-PAT scores(73).  
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3 283 ***Autoimmune conditions:***  
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5  
6 284 Children with autoimmune diseases may have a high tendency to develop ED which was highlighted  
7  
8 285 in a study using a novel technique(74). Atherosclerosis is an emerging cause of morbidity and  
9  
10 286 mortality in patients with rheumatological conditions such as juvenile idiopathic arthritis, SLE and  
11  
12 287 dermatomyositis. Borenstein-Levin et al assessed a cohort with autoimmune conditions compared to  
13  
14 288 controls: 29% in the study group had ED compared to 6% ( $p < 0.05$ )(74). Chang et al noted nocturnal  
15  
16 289 blood pressure (BP) non-dipping is associated with ED in SLE patients highlighting a potential role  
17  
18 290 for ambulatory BP monitoring in these patients(*Table 3*)(8).  
19

20  
21 291 ***Metabolic diseases:***  
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23  
24 292 Yano et al research in Fabry disease patients demonstrated that early diagnosis of ED can help  
25  
26 293 determine the timing of initiating enzyme replacement therapy(75). Utilizing RH-PAT as a screening  
27  
28 294 tool for early renal involvement may be helpful as it may detect abnormalities even prior to  
29  
30 295 microalbuminuria(76). This can provide guidance on enzyme replacement therapy which is required  
31  
32 296 to prevent irreversible progressive renal failure. Al Jasmi et al research in mitochondrial diseases  
33  
34 297 reported that arginine or citrulline supplementation may improve ED, which provides evidence that  
35  
36 298 these amino acids may be therapeutic (*Table 6*)(58).  
37

38  
39 299 ***Inflammatory bowel disease:***  
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41  
42 300 One study (*Table 6*) highlights that IBD patients had lower RHI compared with controls(55). Petr et al  
43  
44 301 (2014) provided evidence of increased ED in children with Crohn's disease compared to healthy  
45  
46 302 controls(77). RHI values were significantly lower in the patients with Crohn's than controls ( $p <$   
47  
48 303 0.05).  
49

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51 304 ***Infectious diseases:***  
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53  
54 305 Dirajlal-Fargo et al used Endo-PAT to assess ED in human immunodeficiency virus (HIV) patients  
55  
56 306 (*Table 6*)(62, 78). Perinatally acquired HIV patients appear to have higher levels of ED (RHI 1.34  
57  
58 307 (1.20, 1.42) compared with controls (1.52 (1.27, 1.80) ( $p < 0.01$ ))(78). The pathogenesis of severe  
59  
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3 308 Plasmodium vivax malaria is poorly understood. ED and reduced nitric oxide (NO) bioavailability  
4  
5 309 characterize severe falciparum malaria. Barber et al (2016) identified that endothelial function was  
6  
7 310 impaired in proportion to disease severity. Those with severe vivax malaria, non-severe and healthy  
8  
9 311 controls median RH-PAT index 1.49, 1.73, and 1.97 respectively (p=0.018)(79). ED in this cohort  
10  
11 312 was associated with reduced L-arginine bioavailability, which may contribute to microvascular  
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13 313 pathogenesis.  
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19 315 **Discussion:**

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22 316 To our knowledge, this study is the first to conduct a rigorous systematic review of published and  
23  
24 317 presented literature on the results of RHI as measured by Endo-PAT 2000 as a measure of endothelial  
25  
26 318 dysfunction in children and adolescents. One of the benefits of RHI as a measure of ED is that it is an  
27  
28 319 easy test to conduct, is well-tolerated by children and adolescents and it can be performed at the point  
29  
30 320 of care.  
31

32  
33 321 Weaknesses of the paper include the quality of the papers are limited and varied; 11 are conference  
34  
35 322 abstracts that had little information available on methods or results and have limited analysis.  
36  
37 323 Observational studies are also limited in research value. Many are case-control studies which are not  
38  
39 324 as valuable as randomised controlled trials (RCT). Only 4 studies are RCTs. The studies cannot be  
40  
41 325 compared for a meta-analysis as most are not RCT level research of high enough quality. Therefore,  
42  
43 326 the conclusions drawn from many of these studies are limited. There are also limitations of RHI as  
44  
45 327 reliable method for defining ED. There is no defined RHI cut off value in paediatric populations.  
46  
47 328 Moreover, there may be significant findings in studies in the grey literature or in conference  
48  
49 329 presentations that was not included, for example in the studies where 25 authors did not respond to  
50  
51 330 emails. Only papers from 2015 to March 2021 were included. Many of the papers did not include  
52  
53 331 other factors that would be important in a cardiovascular assessment of children, for example family  
54  
55 332 history, cholesterol and blood pressure parameters and Body Mass Index (BMI) and standardised BMI  
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57 333 (SDS) measurements. So, in many studies it cannot be excluded that there were confounding variables  
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3 334 affecting the ED score. Regardless, this study indicates that there are a significant number of  
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5 335 published paediatric papers that indicate the presence of ED in children as young as 8 years old.  
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8 336 Strengths of the paper include a comprehensive literature search including contacting authors by email  
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10 337 for separate paediatric results in studies with combined adult and paediatric data. All study types were  
11  
12 338 reviewed and even the studies without results but had interesting points were included in our  
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14 339 discussion. Also, we do not think that this paediatric Endo-PAT review has been done before. Our  
15  
16 340 results highlight that Endo-PAT has benefits including point-of-care and ease of conduct of test for  
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18 341 assessor.  
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20  
21 342 The potential future role of Endo-PAT for paediatric patients may be an adjunct tool in screening for  
22  
23 343 cardiovascular risk factors. If atherosclerosis is identified early, it can be halted in its process in  
24  
25 344 certain conditions. There is huge potential for its use in diabetic patients. Improving glucose control  
26  
27 345 can protect endothelial function. Persistent high sugars can impair endothelial function via oxidative  
28  
29 346 stress and production of free-radicals(2). Lower insulin sensitivity poses a risk of diabetic  
30  
31 347 nephropathy(9). Microangiopathic renal damage increases oxygen consumption and increases  
32  
33 348 resistance in the afferent arterioles. Shah et al report T2D patients have greater vascular thickness and  
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35 349 stiffness and worse endothelial function compared to obese and lean children(80). This is raising  
36  
37 350 concern that adolescents with T2D are already at risk of developing early onset cardiovascular  
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39 351 disease.  
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42  
43 352 Diabetic microangiopathy can result in retinopathy, neuropathy and peripheral vascular neuropathy.  
44  
45 353 Subclinical evidence of these complications can be seen in paediatric patients, especially in those with  
46  
47 354 poor glycaemic control. Unfortunately, there have been reports of T2D paediatric patients diagnosed  
48  
49 355 with microangiopathic complications, particularly nephropathy(81). This early endothelial damage  
50  
51 356 can be linked with increased morbidity and mortality(82). Moreover, new onset diabetes after  
52  
53 357 transplantation (NODAT) is characterised by insulin resistance and T2D(83). Endo-PAT has multiple  
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55 358 benefits in obesity as it can identify if early ED is present and therefore strategies to reverse or halt  
56  
57 359 this process can be made (*Table 2*)(7, 30, 35).  
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3 360 In recent decades, the number of childhood cancer survivors is increasing(84). Treatments utilized  
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5 361 such as haematopoietic stem cell transplantation have increased risk of cardiovascular disease(85, 86).  
6  
7 362 Following chemotherapy, radiotherapy, immunosuppressive treatments the risk of insulin resistance  
8  
9 363 has been noted(87). With advances in treating malignant paediatric conditions there are long term  
10  
11 364 complications emerging in survivors. High dose chemotherapy including anthracyclines, alkylating  
12  
13 365 agents and vinca alkaloids may disrupt the substances on the surface of the endothelium and impair its  
14  
15 366 ability to dilate and constrict. Moreover, total body radiation poses a risk by damaging the elastic  
16  
17 367 matrix. Heart disease in long-term cancer survivors is 5-10 times higher than their siblings(87).  
18  
19 368 Brouwer et al (2013) studied cancer survivor patients after potential cardiovascular toxic treatment  
20  
21 369 (e.g. anthracyclines, platinum) and/or radiotherapy and noted a higher risk of ED compared with  
22  
23 370 sibling controls(88). Jehlicka et al (2011) used Endo-PAT and noted acute lymphoblastic leukaemia  
24  
25 371 (ALL) patients had lower RHI compared to controls ( $1.57\pm 0.50$ ,  $1.96\pm 0.63$ ;  $p\leq 0.05$ )(89).  
26  
27  
28  
29 372 Turner syndrome (TS) patients have increased cardiovascular risk factors which predispose to cardiac  
30  
31 373 and cerebrovascular complications(90). A case-control study on TS patients noted a statistically  
32  
33 374 significant increase in RHI in GH-treated girls(91). There are countless other paediatric syndromes  
34  
35 375 with risk of ED that could benefit from screening.  
36  
37  
38 376 Furthermore, in cardiac diseases and post-cardiac surgery Endo-PAT has been proven useful in  
39  
40 377 multiple studies (*Table 3*)(44, 69, 90). Dietz et al (2015) systematic review and metanalysis on  
41  
42 378 peripheral ED in Kawasaki disease, report coronary arterial aneurysms had higher surrogate markers  
43  
44 379 for cardiovascular disease risk(92). This may indicate these patients should be monitored for CVD in  
45  
46 380 adulthood, however significant heterogeneity was noted. Endo-PAT has been shown to be beneficial  
47  
48 381 postoperatively in Fontan survivors and comparing surgical techniques like in the 'The  
49  
50 382 LOVE-COARCT study' (Long-term Outcomes and Vascular Evaluation After Successful Coarctation  
51  
52 383 of the Aorta Treatment) (93-95).  
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55  
56 384 With the rising premature population, Endo-PAT may prove useful in this cohort. Harris et al (2020)  
57  
58 385 assessed cardiovascular outcomes for those born with very low birth weights (VLBW) <1500g. The  
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3 386 VLBW cohort (n = 229; 71% of survivors) and term-born controls (n = 100), were assessed at age 26-  
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5 387 30 years. The VLBW cohort had lower RHI compared to controls(96). Endo-PAT is also used in  
6  
7 388 haematological conditions. Sivamurthy et al (2009) reported lower RHI in the majority sickle cell  
8  
9 389 disease in a paediatric population (1.53 and 1.71; p value .032). RHI was not normal in children with  
10  
11 390 chronic transfusions or hydroxyurea(97).

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14  
15 391 The psychological studies in our paper raise an interesting link between the vascular system and the  
16  
17 392 psychiatric diagnoses. Retinal vascular calibre was shown to be associated with endothelial function  
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19 393 in bipolar disorder patients and it has been suggested that it may be used as an assessment tool in this  
20  
21 394 cohort.

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23  
24 395 Finally, many paediatric autoimmune conditions are linked with ED(8, 74). In SLE patients, ED may  
25  
26 396 occur from impaired clearance of apoptotic cells, oxidative stress, or B cell activation with different  
27  
28 397 circulating autoantibodies(67). Regular ED assessment in SLE patients has been recommended due to  
29  
30 398 risk of subclinical atherosclerosis(67). Moreover, several factors may impact microvascular function  
31  
32 399 in children, for example puberty, which is of particular interest in our paediatric review. Bhangoo et al  
33  
34 400 report improved RHI in correlation with an increase in Tanner stages and postulated that this may be  
35  
36 401 due to sex steroids(98). If Endo-PAT is used in research in adolescents, age, sex and tanner staging  
37  
38 402 must to be taken in account when reporting RHI results(64).

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#### 43 44 45 404 **Conclusion:**

46  
47 405 There are a number of papers in the paediatric literature describing ED at young ages using Endo-  
48  
49 406 PAT. However, in many cases, there has only been a single cohort study using Endo-PAT. Further  
50  
51 407 studies are required to validate these findings. Additionally, longitudinal studies are required to  
52  
53 408 evaluate how this ED may change as the child ages and their chronic conditions changes. Further  
54  
55 409 studies are also required that will characterise more completely the cardiovascular risk profile of these  
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57 410 children with chronic disease. Consensus on other vascular risk markers that could be included in  
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3 411 future studies is ideal and if accomplished, this would facilitate meta-analyses of studies of conditions  
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5 412 with relatively rare conditions.  
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8 413 The establishment of a threshold RHI for normal or abnormal would be helpful if it correlated well  
9  
10 414 with clinical outcomes. This might be achieved in the future either by meta-analysis of the literature,  
11  
12 415 if outcomes are measured and reported in a standardised manner, or by the conduct of a prospective  
13  
14 416 longitudinal study that follows RHI in childhood to adulthood along with identification of cardiac  
15  
16 417 outcomes. The latter would by its nature require to be a long-term study and would require a repeated  
17  
18 418 iterative process to establish the threshold of normal for RHI, as a continuous variable. Therefore, a  
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20 419 meta-analysis may be preferable. In the short term, a systematic approach to cardiovascular risk  
21  
22 420 assessments should be promoted.  
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33 424 **Statements and declarations:**

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36 425 **a. Authorship contributions:**

37  
38  
39 426 All authors contributed to the initial search strategy protocol. I deLaunois performed the online  
40  
41 427 database search. J Hayden and G McDonnell separately performed a blind screen of the abstracts and  
42  
43 428 analysed the papers. G McDonnell contacted the authors of joint adult and paediatric papers to obtain  
44  
45 429 separate paediatric data. J Hayden wrote the initial manuscript which was revised by C O’Gorman.  
46  
47 430 All authors reviewed the manuscript prior to submission.  
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50  
51 431 **b. Competing interests:** There are no competing interests to declare.  
52

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54  
55 433 commercial or not-for-profit sectors.  
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- 1  
2  
3 434 **d.** Data sharing: search technique and data analysis are available from Rayyan software and the  
4  
5 435 corresponding author.  
6  
7  
8 436 **e.** Competing Interest: No competing interests to declare  
9  
10  
11 437 **f.** Ethical approval: this was not needed as this study was a systematic review and did not involve  
12  
13 438 human participants.  
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18 440 **References:**

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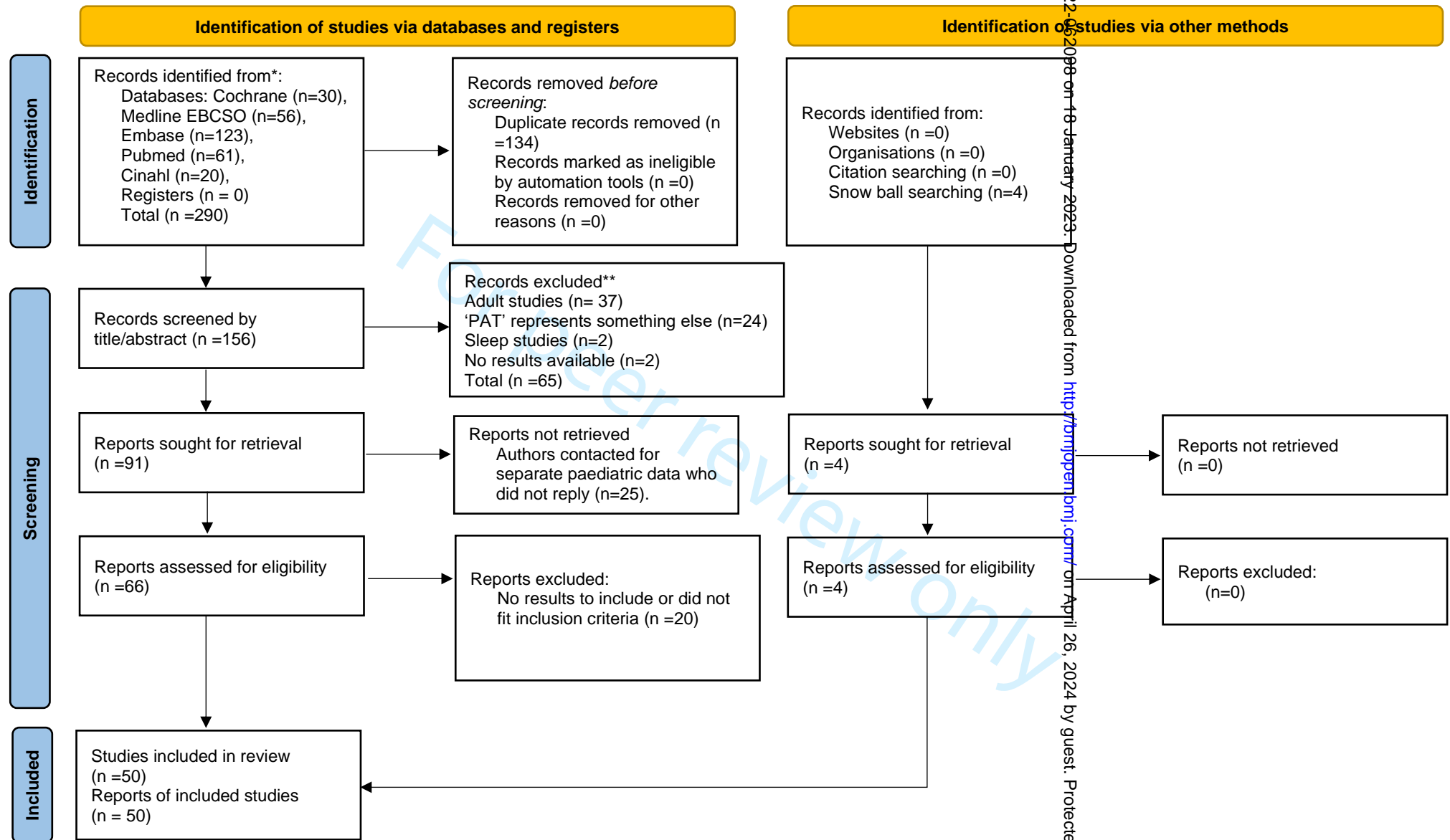
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49 709 Figure 1: PRISMA 2020 Flow diagram of systematic search for Endo-PAT 2000 in paediatric  
50 710 populations.  
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

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# PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			Page
Title	1	Identify the report as a systematic review.	2
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Tables
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analyses, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias(s)).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6



# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Flow diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Nil
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 1-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16
	23b	Discuss any limitations of the evidence included in the review.	17
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	20
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	No response
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Prospero – no response
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Nil
Competing interests	26	Declare any competing interests of review authors.	Nil
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	With authors

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Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71  
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