

Adolescent exercise capacity predicts higher exercise tolerance later in life when compounded by anaemia in patients with pulmonary arteriovenous malformations

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- **What is already known on this topic**

PAVMs develop in childhood/adolescence, cause low oxygen levels (hypoxaemia) and remain ~stable until treatment. Upon diagnosis, children and adults are sometimes advised to restrict exercise.

- **What this study adds**

In adults at a mean age of 56y, exercise tolerance was associated less with oxygen saturation, more with anaemia commonly present due to concurrent hereditary haemorrhagic telangiectasia (HHT), and also with exercise capacity aged 19y. The benefit from modestly increased activity aged 19y was greater than the decrements from severe anaemia or 3 decades of life.

- **How this study might affect research, practice or policy**

Clinicians should not advise patients to restrict exercise based on unsubstantiated assumptions about pathology. Adolescents with PAVMs/in HHT families can be encouraged to exercise more frequently, seeking activities safely pursued by current study respondents, as these are predicted to translate into positive adult health outcomes. There is scope for future research to address this topic by prospectively studying the 'at risk' population of children with a family history of HHT/ PAVMs.

ABSTRACT

Exercise tolerance predicts survival and mental health. To test benefits during adolescence for patients with pulmonary arteriovenous malformations (PAVMs) that cause hypoxaemia, we examined current and retrospective exercise tolerance aged 12y and 19y, linking to clinical records. In the 85 patients (65 female, mean age 56y), current metabolic equivalents ranged from 1.75 to 14.8 (mean 7.85) kcal.kg⁻¹.min⁻¹. Oxygen saturation explained only 2.2% of the variability. There were stronger associations between current exercise tolerance and anaemia indices, particularly the need for blood transfusions. In univariate and multivariate analyses, the strongest anaemia-independent predictor was exercise tolerance aged 19y. In this cohort, the benefit associated with modestly increased activity by 19y (2.9 METs) was greater than the decrements from severe anaemia (~2.54 METs) or 3 decades of life (2.13 METs). The data support enhanced exercise for people with PAVMs, as for the general population, in preparation for later-life health challenges.

BACKGROUND

Regular exercise has multiple physiological benefits including improved mental and physical health. Exercise capacity, that is the amount of exercise an individual can withstand before becoming too tired to continue, is an indicator of good cardiovascular fitness and predicts survival.[1-3] For example, a 1 metabolic equivalent (MET) increase in exercise capacity was associated with mortality reductions of 17% in 5,721 females, [1] 10% in 1,185 men[2], and 26% in 1,545 adults.[3] The ability to exercise declines with age, and with disease processes.[1-3] We hypothesised that increased exercise in earlier life may enhance the resilience of oxygen delivery and exercise capacity in later life, because evidence suggests adaptability and growth of the lung is feasible if challenges occur during childhood or adolescence.[4]

To test, we adapted the non-invasive Veterans Specific Activity Questionnaire (VSAQ) developed by Myers et al [2,3] and applied retrospectively for patients with pulmonary arteriovenous malformations (PAVMs) which develop prepubertally.[5] Previously we showed that anaemia and minor differences in airflow impacted on adult exercise capacity measured by cardiopulmonary exercise testing.[6,7] Anaemia is common in patients with PAVMs because most have hereditary haemorrhagic telangiectasia (HHT) when recurrent nosebleeds and other blood losses lead to iron deficiency.[8]

METHODS

For the current study, a modified VSAQ ([Supplementary Methods](#)) was embedded within a questionnaire ethically approved by NHS HRA London South-East Research Ethics Committee (16/LO/1909). All participants gave informed online consent, and respondents previously seen at our PAVM Reference Centre provided additional consent and dates of birth to link to their medical records.

As previously, SaO₂ was measured after 7-10 minutes standing, reflecting the size of the right-to-left shunt through PAVMs; arterial oxygen content (CaO₂) was calculated by $1.34 \times \text{haemoglobin} \times \text{SaO}_2$; and METs were calculated as $4.74 + (0.97 \times \text{VSAQ score}) - (0.06 \times \text{age})$. [2,3,5-7] Further methodological details are provided in [Supplementary Methods](#).

RESULTS:

Within a total survey response of 259 who provided consent, age, sex and a current VSAQ, the 85 seen at our institution with PAVMs are the focus of the current manuscript. The cohort comprised 65 females, 20 males, with mean age 56y (range 27-77y). Presentation SaO₂ ranged from 76-99.8% (mean 92.7%). Sixty-three (74%) had received treatments and most recent SaO₂ ranged from 86.5-99.8% (mean 95.5%). Seventy-eight (92%) respondents had HHT, in 33 cases, genotype-confirmed (21 *ENG*, 8 *ACVRL1*, 4 *SMAD4*), highlighting the overlapping nature of HHT and PAVMs.

In keeping with British Thoracic Society good practice,[9] only three respondents had their PAVMs diagnosed before the age of 18y, and more were diagnosed by family screens (N=24) and by chance (N=18) than due to health problems potentially attributable to PAVMs (N=25). Of those receiving advice about exercise upon PAVM diagnosis, one-quarter (3/12) had been told to reduce activity. Treatment of PAVMs was reported to improve exercise capacity by 32/62 (47%), with 32 (52%) 'staying about the same', though only two had been treated before the age of 18y (both treated at 17y).

Development of PAVMs is considered to be ~complete by the end of adolescence.[5,9] Most of the cohort (89.4%, 76/85) described being able to pursue school physical education (PE) 'the same or better than' the rest of their class ([Figure 1A](#)), detailing additional sports activities beyond school lessons ([Figure 1B](#)). Only 3/85 (3.5%) selected the "I don't remember" option for participation in school PE lessons around the age of 12y. By 19y, a smaller proportion described themselves as sporty (59%, 50/85, Fisher exact test $p < 0.0001$) though 55% (47/85) described additional sports activities, often pursued to high levels of competition ([Figure 1Bii-iv](#), [Supplementary Figure 1](#)).

As shown in [Figure 2A](#), exercise tolerance as self-reported using the VSAQ varied across all respondents, and was significantly lower at the time of the response than when aged 12 or 19y. Current VSAQ scores ranged from 1 to 13 (median 7, representing needing to stop walking up a hill). Similarly, as shown in [Figure 1B](#), VSAQ-derived METs (which are biomarkers for V[dot]O₂ peak)[2,3,7] reduced with age. At the time of response, these ranged from 1.75 to 14.77 (median 7.63) kcal.kg⁻¹.min⁻¹.

There was no relationship between METs at any age and the presentation SaO₂ (all p-values >0.24). As shown previously,[6,7] stronger associations were provided by haemoglobin, and by CaO₂ which incorporates both haemoglobin and SaO₂ (Table 1, Supplementary Table 1), particularly if restricted to the 57 cases with measurements made within 3 years (Supplementary Table 2). More than 30% of respondents reported requiring blood transfusions or intravenous iron, and these anaemia treatment indices displayed the strongest association with current METs, explaining 10-16.7% of variance with p-values <0.005 (Table 1, Figure 2Ci).

Table 1 also shows that there was no association between current METs and METs aged 12y, but that individuals with higher METs aged 19y had higher METs at later ages. This relationship persisted in multiple regression adjusting for indices of anaemia (Table 1, Figure 2Cii, Supplementary Table 1). In this cohort, we could calculate that the decrement in current exercise tolerance due to severe anaemia (loss of 2.51-2.65 METs) or 3 decades of life (loss of 2.13 METs) would be offset by modest increases in exercise capacity corresponding to 3 points on the VSAQ scale (gain of 2.9 METs).

DISCUSSION

The associations of exercise capacity/tolerance with metrics of anaemia and CaO₂, rather than SaO₂ have been reported in other PAVM populations and provide a further validation of the importance of correcting anaemia for people with PAVMs.

Previous studies have quantified that physical activity declines from adolescence to young adulthood with no predictors explaining variability.[10] The novel finding in this study, albeit based on retrospective data with possible recall bias, was that independent of other health problems, the level of exercise tolerance achieved by 19y predicted the level of exercise tolerance and essentially health in later life. Further, the potential benefit from regular exercise was of similar magnitude to the decrements from anaemia and aging.

One study weakness is that we did not capture a young adulthood timepoint so we cannot suggest adolescence is the only period when exercise would be beneficial. That said, it may be easier to pursue later in adulthood if exercise is already an established lifestyle choice by 19y.[10] Another study weakness is reliance on recollection, although the study specifically chose ages corresponding to school milestones in the UK; options of “do not remember” were rarely used; and it is doubtful that a decades-long prospective study would ever be conducted for this rare condition. Associations between exercise capacity in later and earlier adult life

may not surprise since people commonly form attitudes to regular exercise by the age of 19y. However, this is a cohort with abnormal physiological indices, where many are cautioned against exercising upon diagnosis.

Future studies can examine further cohorts, and the first are in progress. In the meantime, for young people with PAVMs with or without HHT, medical advice can be to encourage rather than discourage sporting activity.

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CONTRIBUTORSHIP

CLS conceived the study and generated the original survey. HI and CLS generated the exercise modified survey. NC, AA, JC, JR and CLS led on patient-facing discussions, assessments and treatment. Interim data analysis was by HD and HI, final data analysis was by CLS. Manuscript text and Figures were generated by CLS. All authors reviewed and approved the final manuscript.

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COMPETING INTERESTS:

No, there are no competing interests for any author.

DATA SHARING

Non-identifiable, aggregated data is currently available on reasonable request from the authors and is being prepared, appropriate to consent for wider access on NIHR Imperial BRC Digital Platforms (*'A Trust-owned, real-world, patient Database Asset for Clinical Decision Support and AI Development from 40 years of PAVM/HHT at Imperial/ICHT'* to Alsafi, Coote and Shovlin, 2024).

PATIENT CONSENT

All participants provided online consent to the initial survey and to data linkages with their medical records.

ETHICAL APPROVAL

Ethical approvals were from the NHS HRA London South-East Research Ethics Committee (16/LO/1909 *"HHT and PAVMs-Wider Medical Issues- Online survey based examination of phenotypes in hereditary haemorrhagic telangiectasia (HHT)"*), and Hammersmith, Queen Charlotte's and Chelsea and Acton Hospital Research Ethics committee (LREC 2000/5764 *"Hammersmith Hospital patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia"*). Participants gave informed consent to participate in the study before taking part.

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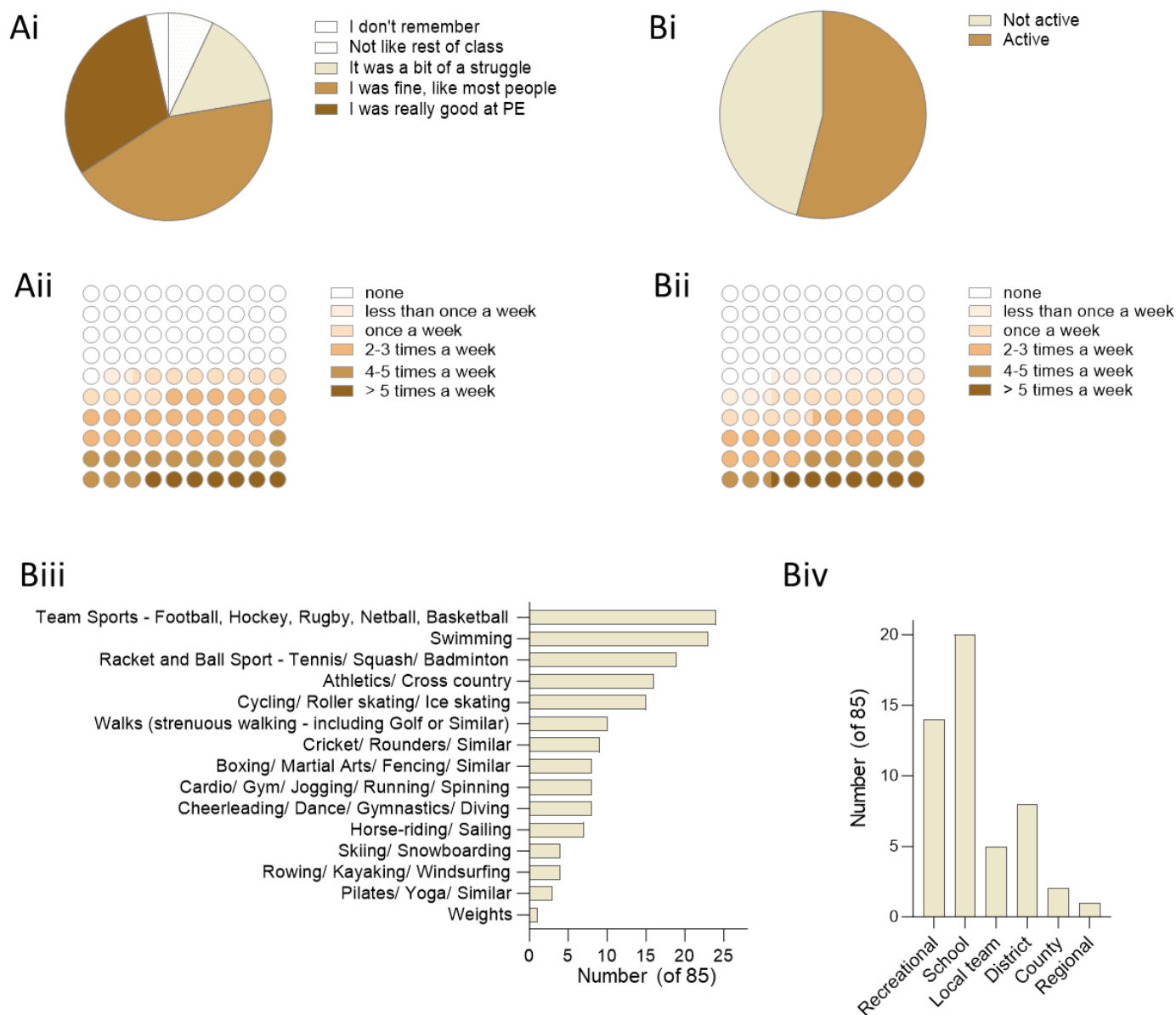
Table 1: Demographics of PAVM cohort, and relationships with current exercise tolerance by univariate and multiple linear regression

		Relationship with current† exercise capacity (METs) kcal.kg ⁻¹ .min ⁻¹					
	Demographic	Univariate (crude regression metrics)			‘Blood’ (red cell) transfusion-adjusted		
		% of METS explained	P value	Regression coefficient (95% confidence intervals)	% of METS explained	P value	Regression coefficient (95% conf intervals)
Binary variables, n (%)							
Female	65 (76)	0.3	0.26	-0.90 (-2.48, 0.80)	18.6	0.089	-1.25 (-2.68, 0.195)
Any interventional PAVM treatment	66 (78)	3.3	0.067	-2.11 (-4.37, 1.53)	16.0	0.11	-1.74 (-3.85, 0.38)
Currently or previously used iron tablets*	67 (79)	10.0	0.002	-2.51 (-4.07, -0.94)	22.3‡	0.01	-1.96 (-3.44, -0.48)
Still anaemic despite using iron tablets	36 (42)	15.5	0.003	-2.53 (-4.13, -0.93)	15.0‡	0.026	-2.12 (-3.99, -0.27)
Use of intravenous iron*	26 (31)	13.4	<0.001	-2.54 (-3.90, -1.17)	18.9‡	0.053	-1.52 (-3.06, 0.015)
Use of blood transfusions*	34 (40)	16.7	<0.001	-2.65 (-3.91, -1.39)	-	-	-
Continuous variables, range (mean [SD])							
Age range, y	27-77 (56 [12.1])	6.7	0.01	-0.071 (-0.13, 0.018)	18.9‡	0.078	-0.047 (-0.099, 0.0053)
Most recent SaO ₂ , %	86.5-99.8 (95.5 [10.9])	2.2	0.099	0.168 (-0.33, 0.36)	22.6	0.068	0.21 (-0.0157, 0.426)
Most recent Hb, g.L ⁻¹	81-176 (131.8 [20.6])	4.5	0.035	0.035 (0.0025, 0.067)	15.9‡	0.54	0.010 (-0.023, 0.044)
Most recent CaO ₂ , mls O ₂ .dL ⁻¹	10.5-21.1 (16.7 [2.5])	6.6	0.014	0.33 (-0.069, 0.59)	18.8‡	0.44	0.108 (-0.166, 0.382)
METs aged 12y, kcal.kg ⁻¹ .min ⁻¹ .	10.81-16.63 (14.3 [2.0])	<0.01	0.31	0.18 (-0.17, 0.53)	12.7	0.30	0.172 (-0.154, 0.49)
METs aged 19y, kcal.kg ⁻¹ .min ⁻¹ .	6.51-16.21 (13.1 [2.7])	3.8	0.047	0.257 (0.0033, 0.511)	18.3	0.03	0.257 (0.023, 0.491)
METS at current† age, kcal.kg ⁻¹ .min ⁻¹ .	1.75-14.77 (7.9 [3.1])	-	-	-	-	-	-

Significant associations defined by $p < 0.05$ are indicated in bold. % of METs explained expresses the adjusted r^2 as a percentage. As ‘blood’ (red cell) transfusion explained the greatest proportion of variance, this was used for multiple regression analyses. ‡ Variables that did not meet regression assumptions as they were non independent of blood transfusions ([Supplementary Table 1](#)). *For anaemia. †27-77y (56y).

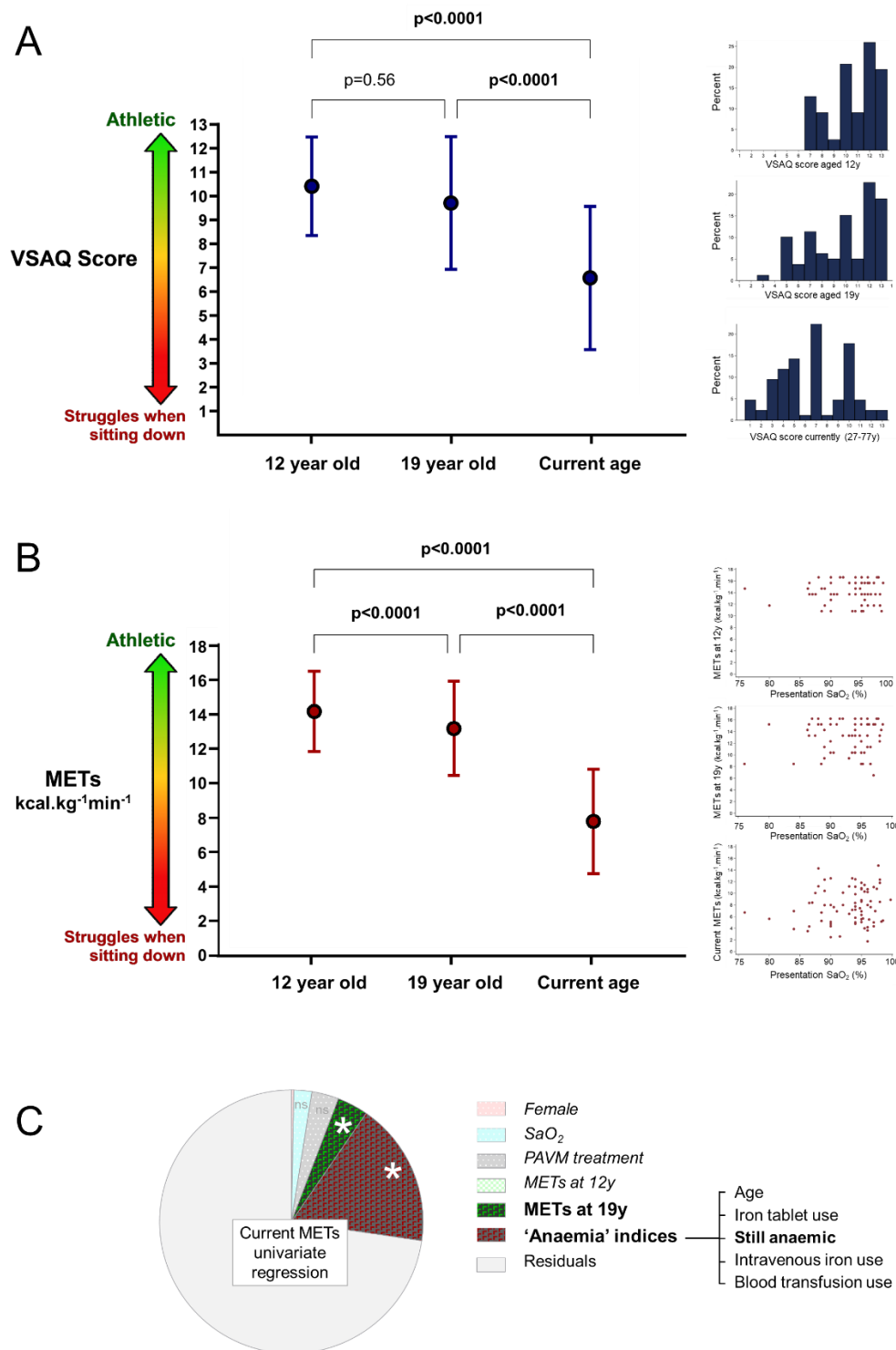
FIGURES

Figure 1:.



Details of exercise activity aged 12 and 19y. Responses to questions **A)** For age 12y: Around the age of 12, **i)** were you able to do school PE/sports lessons like the rest of the class? **ii)** how often did you do sports or exercise outside PE lessons? **B)** For age 19: Around the age of 19 **i)** were you sporty? **ii)** how often did you do sports or exercise outside PE lessons? **iii)** which of these sports or exercise did you do regularly? **iv)** What was the highest level of competition you reached? See Supplementary Figure 1 for further detail.

Figure 2:



Reported exercise tolerance. A) VSAQ scores as reported for 12y, 19y and current age (27-77y, mean 56y). Left graph indicates mean and standard deviation at the 3 ages, with displayed p values calculated by Dunn's test post Friedman. Right graphs indicate percentage of cohort reporting VSAQ score of 1-13 aged 12y (top), 19y (middle) and current age (bottom). **B)** Metabolic equivalents (METs) as calculated from reported VSAQs for 12y, 19y and at current age (27-77y, mean 56y). Left graph indicates mean and standard deviation at the three ages, with displayed p values calculated by Dunn's test post Friedman. Right: two-way graphs of METs on y axis, and presentation SaO_2 on x axis, aged 12y (top), 19y (middle) and current age (bottom). No associations were detected by Spearman (all p values > 0.24) or by regression (all p values > 0.17). **C)** Visual representation of the proportion of current METs explained per variable in univariate regression, with bold text indicating names of variables that met significance in transfusion-adjusted regression (Table 1). Size of pie represents maximum r^2 . White star $p < 0.05$; ns, not significant. As 'anaemia' variables were non independent, only blood transfusion that explained the greatest proportion of variance is displayed here.

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Supplementary Background

We hypothesised that increased exercise in earlier life may enhance the resilience of oxygen delivery and exercise capacity in later life. Higher levels of aerobic fitness and exercise participation throughout childhood and adolescence are known to be associated with increased forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1).¹⁻³ Similarly, evidence suggests adaptability and growth of the lung is feasible if challenges occur during childhood or adolescence, for example, following surgical removal of one lung (pneumonectomy), or residing at higher altitude with ambient hypoxia. In childhood⁴ as in puppies⁵, after pneumonectomy there is evidence for compensatory growth of the remaining lung, and living at altitude is associated with higher lung volumes.⁶⁻⁸ In contrast, adults who move to areas of high altitude after puberty do not develop higher lung volumes,⁷ and older age groups do not demonstrate compensatory growth of the remaining lung post pneumonectomy in humans,⁴ or dogs.⁵

Supplementary Methods

Age adjustments of Veterans Specific Activity Questionnaire (VSAQ):

As previously described,⁹⁻¹² the VSAQ lists 13 exercise categories in order of increasing activity intensity, and participants are asked to indicate the first (lowest) activities where they need to stop. The gives a raw VSAQ score which, when combined with age, can be used to calculate metabolic equivalents at limiting exercise (METs) where 1 MET is defined as the consumption of 3.5 mL of oxygen, per kg of body weight, per minute. The equation used in the original 1994 study of 212 veterans (where 67% of the variance in treadmill performance was explained by age),¹⁰ and as used for earlier studies on patients with PAVMs,^{13,14} was used again in the current study:

$$METs = 4.74 + (0.97 \times VSAQ) - (0.06 \times Age).$$

For the purpose of the current study, the UK-modified VSAQ¹³ was adjusted to enable retrospective evaluation of exercise capacity in childhood. In addition to reporting their current VSAQ, participants were asked to provide a VSAQ as though they were 12 years old (an age correlating with age ranges previously studied in lung function and childhood exercise research)^{3,15} and 19 years old. Twelve was considered the earliest participants would be able to recall their exercise capacity reliably, corresponding with the move from primary to secondary school in the UK, a substantial life event to aid memory recall, and usually during or preceding pubertal growth spurts. Nineteen was selected because 18/19y is the age when PAVMs and alveolar development are considered essentially complete,^{16,17} and the age of 18y is associated with other major life events to aid recall. Minor alterations to wording, highlighted in [Figure S1](#), made the activities relevant to those performed by 12-year-olds.

Imagine you were answering this question around the age of 12. On this list again, please tick any activity that when performed for a period of time, would typically have made you want to stop **when you were 12**.

1	Eating, getting dressed or working at a desk
2	Taking a shower, walking down eight steps
3	Walking slowly on a flat surface for 100-200 metres. Helping with a moderate amount of work around the house such as vacuuming, sweeping the floors or carrying groceries
4	Helping with light gardening work, painting, light carpentry, DIY ('do it yourself') - perhaps in Cub Scouts
5	Walking briskly e.g. four miles per hour. Dancing, washing the family car
6	Pushing a lawn mower. Helping with heavy carpentry. Playing nine holes of golf carrying your own clubs
7	Walking uphill. Performing heavy outdoors work e.g. digging. Tennis singles, picking up and carrying a 4-5 year old child
8	Carrying a toddler up stairs or two heavy bags of shopping (e.g. containing 4-5 large bottles of lemonade). Helping move heavy furniture, jogging slowly on the flat
9	Cycling at a moderate pace, sawing wood (perhaps in Cub Scouts)
10	Brisk swimming, cycling uphill, walking briskly up hill, jogging (around six miles per hour)
11	Carrying a heavy load up two flights of stairs, cycling briskly, cross country skiing
12	Running briskly, continuously
13	Any competitive activity, including those which involve intermittent sprinting. Running or rowing competitively, cycling races

↑ Even the best athletes in your school would have had to tick this last box!

Figure S1: VSAQ adapted for 12-year old relevance. Questions were adapted from the UK-modified VSAQ described by Gawecki et al.¹⁴ Exercise categories were kept the same to enable comparison with V[dot]O₂ peak-validated adult responses.^{9,10,13,14} Additions or alterations to wording, to make the activities more relevant to those performed by 12-year-olds, are highlighted in yellow. Within certain categories (6, 7, 8, 11) the order of activities was re-arranged to promote a more 'child-friendly' activity at the start of the list.

Survey platform:

VSAQs were embedded within a pre-existing patient questionnaire that had previously generated multiple peer-reviewed manuscripts.¹⁸⁻²⁹ For the current study, it was transferred to SurveyMonkey® Enterprise software to meet European GDPR requirements and comprised a potential 184 questions including 46 new questions focused on exercise and activity participation as detailed below. Ethical approvals were given for the original survey, and all amendments.

There were a specific set of questions about school PE, questions recording what sports these did, which they were best at, and what was the highest level of competition that they reached by the age of 18-19 (Fun/social/recreational; School team; A local team; District team [below County]; County team/was in the top 3 or so for my County; competed at Regional level, higher than County; competed at an Elite level for my Country). Participants were asked if they received advice about exercise when they were diagnosed with PAVMs, and if so whether this was “To carry on as normal”; “To reduce or stop the amount of exercise I do” or “To try and increase the amount of exercise I do”. They were then asked “after having PAVM treatment, my ability to do activity and exercise” with the options “Stayed the same”; “Improved”; “Got worse” before asking for details of exact exercise types that improved.

As approved in 16/LO/1909, the survey was circulated with a specific invitation letter to increase the proportion of patients for clinical data cross-referencing to patients with PAVMs reviewed at our institution between 01/01/2018 – 01/01/2020. To reach wider cohorts (the subject of a separate manuscript in preparation), the study was also advertised via social media on a HHT patient support group; in a research newsletter; and distributed to HHT and PAVM patients with their clinical letters. The survey opened on 28 April 2021, and remained open for ongoing data collection until 15 May 2022 when final data were downloaded. For respondents consenting to medical records linkage, dates of birth were independently linked to clinical notes via the Trust’s Picturing and Archiving Communication System (PACS), filtering by date of birth and referring clinician. Survey responses were then cross-checked against clinical notes for name, age, sex, and PAVM/HHT status before capturing the earliest and most recent haemoglobin, SaO₂, and relationship to embolization or surgical treatment.

Data Analysis:

Survey data were downloaded in csv format, cleaned and transformed to numeric data in Microsoft Excel, and imported to STATA v15.0 (Statacorp, Texas) and GraphPad Prism version 10 for Windows (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com), for analysis.

Cross referencing with medical records identified two duplicate responses – for one individual who supplied a second “current” VSAQ months later after a deterioration in clinical status due to a non PAVM confounder: their initial record was used. The second individual had submitted virtually identical responses relevant to the current study, and again, the first entry was used as closer to the blood and SaO₂ measurements.

Where individuals had gaps in their VSAQ responses, e.g. had ticked only two widely-spaced categories but not the intervening categories, the VSAQ score was generated using the lowest category ticked, as had been validated previously in the general²⁵ and PAVM^{14,30} populations. Other missing data variables were treated as unknown (.): to prevent bias, positive responses were expressed as the percentage of the full cohort.

Descriptive statistics were calculated and graphed. Comparative statistics used non parametric tests (for two groups Mann Whitney; for 3 groups Friedman (paired data) or Kruskal Wallis (unpaired data), with Dunn’s post-test corrections). Relationships were initially examined by Spearman correlations. Following confirmation of normal distributions for METS aged 12y, METs aged 19y, and METs current using normal quantile (QQ) plots ([Figure S2](#)), univariate and multivariate regression analyses were performed.

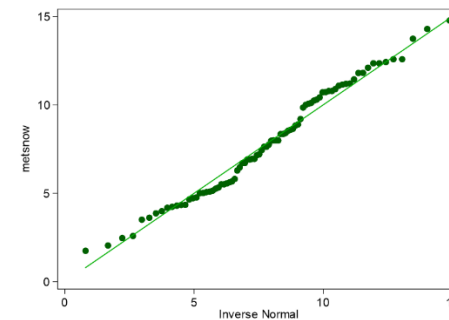


Figure S2: Normal quantile plot of “current metabolic equivalents (METs)”, corresponding to the VSAQ score at the time of questionnaire completion. The graph indicates correspondence between values obtained and values predicted if METs were normally distributed. The variable was therefore considered appropriate to use as the dependent variable in the univariate and multivariate regression analyses described in the main text. Similar distributions were observed for METs aged 12y and METS aged 19y.

Supplementary Table 1: Multivariate regression model considerations

A) Spearman correlations for relationships between measured variables and blood transfusions

<i>Table 1 variables</i>	Spearman rho	Spearman p-value
Female	-0.113	0.30
Any interventional PAVM treatment	0.125	0.28
Currently or previously used iron tablets*	0.188	0.085
Still anaemic despite using iron tablets	0.509	0.0001
Use of intravenous iron*	0.516	<0.0001
Use of blood transfusions*	1.000	<0.0001
Age range, y	0.273	0.012
Most recent SaO ₂ , %	0.035	0.757
Most recent Hb, g.L ⁻¹	-0.412	0.0002
Most recent CaO ₂ , mls O ₂ .dL ⁻¹	-0.451	<0.0001
METS aged 12y, kcal.kg ⁻¹ .min ⁻¹ .	-0.017	0.883
METS aged 19y kcal.kg ⁻¹ .min ⁻¹ .	0.0086	0.940
METS at current age [†] , kcal.kg ⁻¹ .min ⁻¹ .	-0.426	0.0001

B) Multivariate model where independent variables all meet individual significance

<i>Relationship with current METs</i>	Regression coefficient	95% confidence intervals	Individual term P value
Blood transfusion for anaemia	-2.03	-3.23, -0.825	0.001
METS aged 19y	0.330	0.116, 0.545	0.003

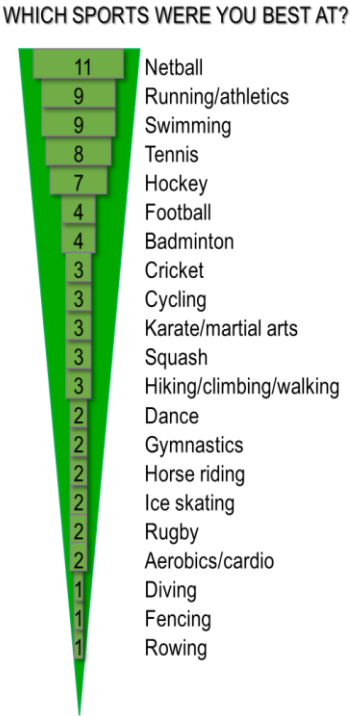
Supplementary Table 1: A) Illustration of relationships between measured variables and blood transfusions. Shaded variables are non-independent. **B)** The only model from the independent variables where all individually met statistical significance for a relationship with current METs, after adjustment for other variables in the model (N=78, adjusted R-squared 0.18, p=0.0002).

Supplementary Table 2: Demographics of cohort with measurements within 3y of survey, and relationships with current exercise capacity

	<i>Number of measurements</i>	<i>Variable demographics</i>	<i>% of METS explained (from adj R-squared)</i>	<i>P value</i>	<i>Regression coefficient (95% confidence intervals)</i>
<i>Continuous variables, range (mean)</i>					
Age range (mean), y	57	28-77 (57)	7.0	0.026	-0.078 (-0.15, -0.0095)
Most recent SaO ₂ (mean), %	56	86.5-99.75 (95.5)	1.8	0.158	0.195 (-0.078, 0.469)
Most recent Hb (mean), g.L ⁻¹	56	81-176 (129)	9.82	0.011	0.49 (0.012, 0.86)
Most recent CaO ₂ (mean), mls O ₂ .dL ⁻¹	55	10.5-21.1(16.4)	14.6	0.002	0.48 (0.178, 0.8776)
<i>Binary variables, n (%)</i>					
Female, (%)	57	47 (81)	<0.01	0.59	-0.57 (-2.66, 1.52)
Any interventional treatment, (%)	57	49 (58)	8.1	0.024	-4.9 (- 9.1, -0.66)
Still anaemic despite using iron tablets	57	26 (31)	21.1	0.002	-2.87 (-4.66, -1.08)
Use of intravenous iron	56	16 (19)	9.5	0.012	-2.26 (-4.01, -0.52)
Use of blood transfusions*	57	22 (39)	6.53	0.033	-6.16 (-1.18, -0.05)
Once		10 (18)			
2-4 times		4 (7)			
5-10 times		3 (5)			
11-50 times		2 (4)			
>50 times		3 (5)			

Supplementary Table 2: Demographics of PAVM cohort of 57 with measurements within 3y of the survey.
In univariate regression analyses, significant associations defined by $p < 0.05$ are indicated in bold. Note restricting to within 1y reduced the cohort to $n=15$ and significance of relationships was not observed in such a small subcohort.

Supplementary Figure 1: Sporting activities pursued to higher levels in patients with pulmonary AVMs



The 85 participants (65 female) had been asked to state which sports they were best at under the age of 19y.
The number reporting each sport is highlighted in the figure on the left, and the type of sport that they described is listed on the left.

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