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## Sex-difference in stroke outcome in young people in relation to haemoglobin level

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Short title: Stroke outcome and haemoglobin in young women

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### Abstract

**Introduction:** Worse stroke outcome in women than men is partly explained by differences in age, aetiology and pre-morbid disability, but lower haemoglobin (Hb) could also contribute, particularly at younger ages. We therefore aimed to explore whether lower Hb levels might correlate with stroke outcome in younger women.

**Methods:** In a population-based cohort (Oxford Vascular study) we studied all patients aged  $\leq 55$  years with a stroke between 1<sup>st</sup> April 2002 and 31<sup>st</sup> March 2023 and face-to-face follow up at one-month. We used ordinal multi-regression models to assess one-month post-stroke modified Rankin Scale score (mRS), and the change from pre-morbid status ( $\Delta$ mRS), in relation to Hb levels (continuous and by WHO definition of anaemia) and sex, with adjustment for age, vascular comorbidities, pre-morbid mRS and medications.

**Results:** Among 348 patients (mean/SD age = 45.4/8.01; 149 female, 42.8%) anaemia was associated with a higher post-stroke mRS (adjusted OR=3.18, 95%CI =1.66-6.06,  $p < 0.001$ ) and greater  $\Delta$ mRS (adjusted OR=2.72, 1.39-5.30,  $p = 0.003$ ). These trends were consistent in both women and men analysed separately and in those with ischaemic stroke only. Women had higher one-month mRS compared with men (adjusted OR=1.58, 1.05-2.38,  $p = 0.03$ ), but further adjustment for the sex difference in Hb (mean/SD Hb: 13.12/1.64 g/dl in women vs 15.13/1.36 in men,  $p < 0.001$ ) removed the effect of sex (fully adjusted OR=1.07, 0.65-1.74,  $p = 0.80$ ). The higher  $\Delta$ mRS in women (adjusted OR=1.57, 1.04-2.38,  $p = 0.03$ ) also diminished after adjustment for Hb (fully adjusted OR=1.04; 0.64-1.70,  $p = 0.87$ ).

**Conclusion:** Low Hb levels are associated with a poor outcome after stroke and could be a clinically important determinant of the sex-difference in stroke outcome at younger ages. If confirmed, these findings further justify correction of iron-deficient anaemia at the population level and in situations where stroke risk is increased.

## Introduction

Women have a poorer functional outcome after stroke, worse levels of depression and lower quality of life than men.<sup>1-4</sup> This sex-difference appears to be at least partly accounted for by pre-morbid factors, such as older age and lower pre-stroke function in women,<sup>2,4-6</sup> and it therefore remains uncertain whether there is a genuine independent sex difference in stroke severity or outcome. Indeed, the paradoxical finding of a lower case-fatality but a worse functional outcome in women versus men has also been reported in several studies.<sup>1,7</sup> However, interpretation of such data is often limited by a lack of stratification by age. Only a few studies have reported outcomes in younger age groups, which should be less confounded by sex-differences in premorbid function, but they do suggest a worse functional outcome after stroke in younger women,<sup>8,9</sup> and there is also evidence of a higher operative mortality and worse neurological outcome after cardiac surgery at younger ages in women.<sup>10,11</sup> One hypothesis that could explain a worse stroke outcome in women, particularly at younger ages, could be increased cerebral susceptibility to ischaemia due to lower haemoglobin (Hb) levels in pre- and peri-menopausal women, related to iron deficiency. Indeed, in a previous study, we showed that lower Hb largely accounts for a compensatory increase in cerebral blood flow (CBF) in younger women (Supplementary Figure 1).<sup>12</sup> Low Hb levels are independently associated with poorer post-stroke recovery and higher mortality in both men and women,<sup>13-15</sup> probably due in part to larger acute infarct volume and growth,<sup>16</sup> and it has been suggested previously that sex-differences in Hb could contribute to the sex-difference in stroke severity and outcome.<sup>17</sup> If so, such sex-difference would be expected to be driven by younger patients, where the sex-difference in Hb is greatest.<sup>12</sup> Given that iron-deficient anaemia is common, simple to diagnose on screening, and relatively easy to treat,<sup>18</sup> it is important to understand any independent effect on stroke outcome. We therefore investigated the association between Hb level and stroke outcome in patients aged  $\leq 55$  years, adjusted for pre-morbid function, in a population-based stroke incidence study to test the hypothesis that lower Hb levels in young women might have a detrimental effect.

## Methods

The Oxford Vascular Study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events, irrespective of age, in a population registered with around 100 general practitioners (GPs) in nine general practices in Oxfordshire, United Kingdom, as described in detail elsewhere (Supplementary Methods).

For the purpose of this sub-study, we included consecutive patients aged between 18 and 55 years with a first stroke between 1<sup>st</sup> April, 2002 and 31<sup>st</sup> March, 2023 who had clinical assessment at presentation and at follow-up one month later (the first main follow-up point in the OXVASC study), and at least one Hb measure at the time of their stroke. Where multiple Hb levels were recorded, the level measured closest after stroke onset was used, usually on the day of hospital admission or clinic assessment. The most recent pre-morbid Hb level was also collected from primary care and hospital records where available. Ferritin levels were measured in a sub-study between 2002 and 2012. To reliably address sex-differences in severity outcomes we included the full spectrum of symptomatic ischemic strokes, including minor strokes with no measurable deficit where patients felt that symptoms had not fully resolved.

### Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by sex (defined as sex assigned at birth) and anaemia status. To avoid data-dependent stratification of our analysis, we used the WHO sex-specific definition of anaemia (Hb < 12g/dL for women and Hb < 13 g/dL for men) although it has been criticised as arbitrary.<sup>19</sup>

Age-adjusted differences in sex and anaemia status for binary variables were assessed through binary logistic analysis. The correlation between Hb measured at the time of stroke and the closest pre-morbid value (when available) was assessed via linear regression and mean values were compared. Ordinal regression was used to assess sex-differences in mRS at one-month post-stroke adjusting for pre-morbid mRS and NIHSS as well as for comorbidities, age and ongoing medical treatment (antithrombotic and antihypertensive). To account for pre-morbid disability, we also assessed changes in mRS score between pre-morbid score and at one-month ( $\Delta$ mRS) as an ordinal variable.

To study the effect of Hb levels on sex-differences in mRS at one month post-stroke and in  $\Delta$ mRS, ordinal logistic regression models without (Model A) and with (Model B) Hb were developed. NIHSS was included in the model as an ordinal variable. To further explore the role of Hb levels on sex-differences in stroke outcome, we studied mRS at one month post-stroke and  $\Delta$ mRS in anaemic versus non-anaemic patients using ordinal regression models. Sensitivity analyses were conducted by sex, and on patients with ischaemic strokes only, with known levels of platelets, and on women on hormonal contraceptive or replacement therapy.

SPSS version 27 was used for all analyses.

### Results

Of 360 potentially eligible patients, three had no Hb available and a further nine had no post-stroke mRS. Among the remaining 348 (96.7%) patients included in the analyses (mean/SD age= 45.4/8.01; 42.8% female), 275 (79%) had ischaemic stroke.

In 150 (43.1%) patients, a premorbid Hb level was also available. Although the mean (SD) time from the pre-morbid measurement to stroke onset was 48.47 (55.12) months, there was a strong linear correlation with Hb at the time of the stroke ( $R^2=0.50$ ;  $p<0.001$ , Supplementary Figure 2), with no significant difference in mean levels (13.83 vs 14.05,  $p=0.06$ ).

Using the WHO anaemia definition, 31 (20.8%) women were anaemic based on their first post-stroke Hb compared with 10 (5.0%) men (OR, 4.66; 95%CI=2.20-9.92,  $p<0.001$ ). Anaemic patients were less likely to be smokers, more likely to have history of valve heart disease, diabetes, or antithrombotic and antihypertensive medication, and had a marginally higher frequency of haemorrhagic strokes and cardioembolic ischaemic strokes (Supplementary Table 1).

#### *Haemoglobin and stroke outcome*

Anaemia at the time of stroke was associated with higher NIHSS (age and sex-adjusted OR=2.10, 95%CI=1.10-3.90,  $p=0.02$ ) and with higher mRS at one-month post-stroke (age and sex-adjusted OR=3.92, 2.12-7.25,  $p<0.001$ ), even after full adjustment for other potential confounders (OR=3.18, 1.66-6.06,  $p<0.001$ ), and with a greater increase in mRS from pre-morbid levels to one-month follow-up (age and sex-adjusted  $\Delta$ mRS OR=2.19, 1.20-4.04,  $p=0.011$ ; fully adjusted OR=2.72, 1.39-5.30,  $p=0.003$ ) (Figure 1 and Supplementary Table 2). These trends were consistent in women and men analysed separately (Supplementary Table 2), and in patients with ischaemic strokes only (Supplementary Table 3).

### *Haemoglobin and sex-difference in stroke outcome*

In addition to the greater prevalence of anaemia in women, ferritin levels were also lower in women (n=41) than in men (n=58), (mean/SD ferritin=77.16/90.31 ng/mL vs 214.26/179.62 ng/mL respectively,  $p<0.001$ ). Women were on average also slightly younger than men (Table 1), but after adjustment for age, there were no sex-differences in vascular co-morbidities, antihypertensive or antiplatelet medications, pre-morbid mRS, ischaemic stroke subtype, or acute care, including recanalization treatments.

Although there was no correlation between NIHSS and sex (Table 1), women did have a higher one-month post-stroke mRS score (age-adjusted OR=1.76; 1.19-2.60,  $p=0.01$ ) which remained after adjusting for pre-morbid mRS, NIHSS, comorbidities and medication (adjusted OR=1.58, 1.05-2.38,  $p=0.03$ ; Table 2, Model A and Figure 1). However, this sex-difference was reduced after further adjustment for Hb level (fully adjusted OR=1.07, 0.65-1.74,  $p=0.80$ ; Figure 1 and Table 2, Model B). Results did not change when adjusting for platelet count in the subgroup of patients with available measures (N=184; adjusted OR, 2.07, 1.10-3.92,  $p=0.03$ ; fully adjusted OR, 1.45, 0.70-3.03,  $p=0.32$ ). Use of oral contraception or hormone replacement therapy in women was unrelated to one-month post-stroke mRS (adjusted by age, pre-morbid mRS, NIHSS, vascular comorbidities and medication, OR= 1.20, 0.65-2.25,  $p=0.57$ ; fully adjusted OR, 1.14; 95%CI 0.61-2.14,  $p=0.68$ ). Despite pre-morbid disability being low in this cohort of young patients (mRS $\geq$ 3 in 16/348, 4.6%), pre-morbid mRS, NIHSS and Hb levels were the only independent predictors of post-stroke disability on multivariable analysis.

The increment in mRS from pre-morbid levels to one-month follow-up was also greater in women than men (mean/SD  $\Delta$ mRS= 1.62/1.46 vs 1.24/1.29 respectively, age-adjusted  $p=0.01$ ). This sex-difference also remained after adjusting for pre-morbid mRS, NIHSS, comorbidities and medication (adjusted OR=1.57, 1.04-2.38,  $p=0.03$ ), but was again significantly attenuated when further adjusted for Hb (fully adjusted OR=1.04; 0.64-1.70,  $p=0.87$ , Supplementary Table 4).

### **Discussion**

In this study on stroke patients aged  $\leq$ 55 years, we showed that those with anaemia (predominantly women) had worse post-stroke outcome and higher mortality, independent of baseline function. Previous studies have reported an inverse correlation between Hb levels and post-stroke mortality and disability without stratification by age,<sup>14,15</sup> and one study suggested that lower Hb levels may play a role in the sex-difference in stroke outcome.<sup>17</sup> However, this study looked mainly at an older population, where sex-differences in Hb are smaller and anaemia is more likely to be confounded by inflammation, cancer or kidney disease.<sup>20</sup> By focussing on a younger population, in which the predominant cause of anaemia in women is iron deficiency,<sup>18,19</sup> we are likely to have reduced unmeasured confounders.

We found that post-stroke outcome appeared to be worse in young women than in men, even when adjusting for age, sex, pre-morbid mRS, NIHSS, co-morbidities and prior medication. However, this sex-difference was lost after further adjustment for Hb levels, suggesting that differences in Hb could explain much of the sex-difference in post-stroke outcome.

Given the association between iron deficiency and thrombocytosis,<sup>21</sup> which could contribute to stroke pathophysiology and outcome, we showed that adjustment for platelets levels did not diminish the effect of Hb on the sex-difference in stroke outcome. Given that hormonal therapy is sometimes used to treat excessive menstrual bleeding, we also did appropriate adjustment for such treatment.<sup>22</sup>

Although we think that the association between low Hb and worse stroke outcome at younger ages is unlikely to be substantially confounded, the mechanism remains speculative. Lower Hb levels have been shown to be independently associated with larger acute infarcts and higher infarct growth, potentially due to reduced ability of the ischemic brain to increase oxygen extraction in the context of hypoxia, when compensatory vasodilation is already exhausted by anaemia;<sup>16</sup> indeed, we previously showed that age-dependent sex-differences in CBF were related to Hb levels.<sup>12</sup> However, other possible mechanisms include increased blood turbulence around the occluded vessel, with facilitated thrombus migration, or hyperdynamic circulation, with upregulation of endothelial adhesion molecules, increased inflammatory response and thrombosis.<sup>15</sup> Under-prescription of antithrombotic medications in anaemic patients could also play a role,<sup>15-17</sup> although in our study anaemic patients were marginally more likely to be on antithrombotic medications.

Our findings in younger stroke patients are consistent with reports of worse outcomes in younger women after cardiac surgery,<sup>10,11</sup> which was largely unexplained even after accounting for sex-differences in pre-existing conditions such as diabetes, heart failure, ventricular dysfunction, kidney or valve disease.<sup>10,11</sup> These studies did not include Hb levels, but in other studies of pre-operative anaemia and coronary artery bypass outcome across all age groups, anaemia was associated with higher fatal and non-fatal outcomes, particularly neurological and

renal, even after adjusting for associated co-morbidities.<sup>23</sup> Moreover, effective pre-operative treatment of anaemia lead to higher day-of-surgery Hb, reduced red blood cells transfusion rates, shorter hospital stay, lower complication rates and mortality.<sup>18,24</sup>

Although anaemia is easy to detect and its underlying causes are largely correctable, it affects up to 2.36 billion of people worldwide. High risk groups include women of reproductive age, children, surgical patients, people with chronic and infectious diseases, and older hospitalised patients.<sup>18</sup> Our findings support global health policies on screening and treatment of anaemia,<sup>18</sup> particularly in younger women, and justify future trials to correct causes of anaemia in groups of patients at higher risk of stroke. One important area for future research would be any association between low Hb and risk and severity of recurrent events in the weeks after TIA and minor stroke, which could be amenable to trials of correction by iron infusion or blood transfusion.

Our study also has some limitations. Firstly, most patients in this cohort did not have CBF/vasomotor reserve measures, making the link between sex, low Hb levels, reduced vasomotor reserve and worse outcome only speculative. However, in our previous study,<sup>12</sup> we showed that Hb largely accounts for higher CBF and lower cerebrovascular resistance index in women. High CBF in the face of low cerebrovascular resistance suggests vasodilation with reduced residual dilatory reserve, in line with our hypothesis.<sup>12</sup> Secondly, outcome was measured with the mRS, with its well-recognised limitations. However, the mRS is widely used as primary outcome measure even in acute stroke trials, allowing comparison between different studies.<sup>6</sup> Thirdly, our analysis was based on Hb measured at the time of the stroke, which might be altered by dehydration or other stroke-related factors.<sup>25</sup> However, we showed that pre-morbid Hb levels, where available, were very similar to those at the time of the stroke. Fourthly, we have focussed on a short-term post-stroke outcome to test the biological plausibility that low Hb levels could have detrimental effect in young women due to reduced compensatory vasodilatory reserve; this hypothesis needs to be explored on larger numbers and long-term. Lastly, the OXVASC study population is mostly Caucasian and therefore our results may not be entirely generalizable to non-Caucasian populations.

To conclude, in this cohort of younger stroke patients, lower levels of Hb accounted for worse stroke outcome in women. If confirmed, these findings further justify correction of iron-deficient anaemia at the population level and in situations where stroke risk is increased.

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#### **Statement of Ethics**

OXVASC was reviewed and approved by the Oxfordshire Research Ethics Committee (OREC A: 05/Q1604/70). All participants gave written informed consent or study assent was obtained from next of kin if the patient was unable to consent.

#### **Conflict of Interest Statement**

The authors report no competing interests.

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#### **Author contributions**

Sara Mazzucco conceived the study, collected the data, did the statistical analysis and interpretation, wrote and revised the manuscript.

Ramon Luengo-Fernandez collected the data and revised the manuscript.

Peter Rothwell conceived and designed the overall study, provided study supervision and funding, acquired and interpreted the data, and revised the manuscript.

#### **Data availability**

The data that support the findings of this study are not publicly available due to privacy reasons but are available from Professor Peter Rothwell ([peter.rothwell@ndcn.ox.ac.uk](mailto:peter.rothwell@ndcn.ox.ac.uk)) upon reasonable request.

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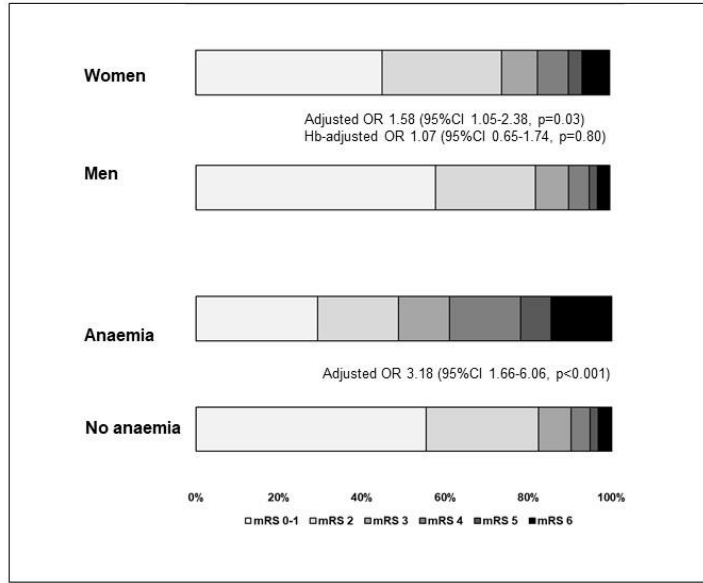
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**Figure Legend**

Fig.1. mRS one month post-stroke by sex and by anaemia status according to the WHO criteria (Haemoglobin <12g/dL for women and <13 g/dL for men).

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	<b>Women N=149</b>	<b>Men N=199</b>	<b>P*</b>
Age, Mean/SD	44.12/8.43	46.44/7.55	0.007
Hb g/dL, Mean/SD	13.12/1.64	15.13/1.36	<0.001
Anaemia (WHO definition)	31 (20.8)	10 (5.0)	<0.001
NIHSS 0-1	81 (54.4)	100 (50.3)	0.67
NIHSS 2-3	23 (15.4)	56 (28.1)	
NIHSS ≥4	45 (30.2)	43 (21.6)	
Pre-morbid mRS, Mean/SD	0.44/0.77	0.38/0.80	0.42
Ischaemic events	106 (71.1)	169 (84.9)	0.004
<b>Ischaemic stroke subtypes</b>			
Cardioembolic	15 (14.7)	18 (11.0)	0.14
Large Artery Atherosclerosis	3 (2.9)	17 (10.4)	
Multiple aetiologies	2 (2.0)	0 (0)	
Other causes	15 (14.7)	17 (10.4)	
Small Vessel Disease	19 (18.6)	37 (22.6)	
Undetermined	40 (39.2)	69 (42.1)	
Unknown	8 (7.8)	6 (3.7)	
<b>Pre-morbid vascular co-morbidities</b>			
Hypertension	32 (21.5)	60 (30.2)	0.17
Diabetes	11 (7.4)	17 (8.5)	0.88
Hyperlipidaemia	19 (12.8)	36 (18.1)	0.31
Current smoking	48 (33.6)	82 (42.3)	0.18
Atrial fibrillation: History of AF	2 (1.3)	4 (2.0)	0.65
New AF on ECG/ECG monitoring	6 (4.0)	6 (3.0)	
Angina	3 (2.0)	5 (2.5)	0.91
Heart valve disease	3 (2.0)	4 (2.0)	0.92
Heart failure	4 (2.7)	1 (0.5)	0.09
TIA	1 (0.7)	5 (2.5)	0.31
Stroke	0 (0)	2 (1.0)	0.99
Myocardial infarction	1 (0.7)	5 (2.5)	0.29
Peripheral vascular disease	2 (1.3)	5 (2.5)	0.45
<b>Pre-morbid medication</b>			
Antithrombotics	17 (11.4)	21 (10.6)	0.67
Antihypertensive medications	28 (18.8)	48 (24.1)	0.51
Statins	10 (6.7)	29 (14.6)	0.07

Independent Variables	Model A (without Hb)		Model B (with Hb)	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age	1.01 (0.98,1.04)	0.53	1.01 (0.99,1.04)	0.34
Sex	<b>1.58 (1.05,2.38)</b>	<b>0.03</b>	1.07 (0.65,1.74)	0.80
Pre-morbid mRS	<b>2.39 (1.81,3.18)</b>	<b>&lt;0.001</b>	<b>2.26 (1.71,3.00)</b>	<b>&lt;0.001</b>
NIHSS 0-1	1		1	
NIHSS 2-3	1.45 (0.87,2.42)	0.15	1.42 (0.85,2.36)	0.18
NIHSS ≥4	<b>9.42 (5.51,16.12)</b>	<b>&lt;0.001</b>	<b>9.00 (5.25,15.41)</b>	<b>&lt;0.001</b>
History of diabetes	0.78 (0.35,1.71)	0.53	0.84 (0.38,1.87)	0.67
History of hyperlipidaemia	1.19 (0.65,2.20)	0.57	1.14 (0.62,2.10)	0.69
Current smoking	1.38 (0.91,2.09)	0.13	1.24 (0.82,1.89)	0.31
Atrial fibrillation	0.93 (0.62,1.41)	0.74	0.92 (0.61,1.39)	0.69
Angina	0.77 (0.17,3.42)	0.73	0.74 (0.17,3.32)	0.70
Heart valve disease	1.76 (0.38,8.12)	0.47	2.73 (0.59,12.76)	0.20
Heart failure	0.23 (0.04,1.41)	0.11	0.22 (0.04,1.32)	0.10
Pre-morbid TIA	2.92 (0.59,14.61)	0.19	2.78 (0.55,13.94)	0.22
Pre-morbid stroke	8.75 (0.52,145.91)	0.13	9.11 (0.54,152.32)	0.12
Pre-morbid myocardial infarction	2.01 (0.42,9.67)	0.38	1.79 (0.38,8.66)	0.47
Peripheral vascular disease	0.36 (0.08,1.59)	0.18	0.36 (0.08,1.56)	0.17
Antithrombotic therapy	0.69 (0.34,1.42)	0.31	0.68 (0.33,1.40)	0.29
Antihypertensive therapy	1.55 (0.91,2.63)	0.11	1.70 (1.00,2.91)	0.05
Hb			<b>0.81 (0.71,0.94)</b>	<b>0.004</b>

Table 2: Ordinal regression analysis exploring predictors of mRS at 1 month post-stroke. Model A: adjustment for age, sex, NIHSS, pre-morbid mRS, vascular comorbidities and medication. Model B: full adjustment for haemoglobin. NIHSS= National Institute of Neurological Disorders and Stroke Scale; mRS=modified Rankin Scale, Hb=haemoglobin.