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Digit ratio (2D:4D), myocardial infarction and fibrinogen in men

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ARTICLE INFO

1. Introduction

Digit ratio (the relative lengths of the 2nd and 4th digits or 2D:4D) is thought to be a negative correlate of prenatal testosterone and a positive correlate of prenatal oestrogen [1,2]. Evidence for these associations comes from experimental studies with non-human animals [2], but there are also correlational data from human prenatal and perinatal studies that report normal levels of testosterone and oestrogen [3]. The 2D:4D is not associated with baseline levels of testosterone in adults [4]. However, with regard to one form of 2D:4D, i.e. right-left 2D:4D (Dr-l), there are reports of negative associations with the magnitude of testosterone-spikes that occur after physical and/or behavioural challenges [5,6]. In common with 2D:4D, low Dr-l is linked to left-handedness and the side differences in 2D:4D are thought to arise as a result of high right-side sensitivity to prenatal sex steroids. Thus, there is evidence that Dr-l correlates negatively with prenatal testosterone and positively with prenatal oestrogen [7].

The incidence of myocardial infarction (MI) shows sex differences, males > females with a 3 to 4 fold excess in men which reduces with age [8]. The 2D:4D also shows sex differences (males < females) with a low to medium effect size (Cohen's d = 0.20 to 0.50, [7]). MI in men is associated with low levels of endogenous testosterone with a weak reduction in risk of about 0.90 for a change of one standard deviation in total testosterone level [9–12]. However, it is not known whether the propensity to produce testosterone-spikes on challenge is related to risk of MI. Considering these associations, Manning and Bundred re-ported a weak negative relationship between right 2D:4D and MI in a sample of 151 men, and suggested that low prenatal testosterone and high prenatal oestrogen (high 2D:4D) may predispose men to early MI [13]. The negative association they described for right 2D:4D explained 13% of the variance in age at MI (p = .001) after risk factors for MI such as BMI, smoking habits and socioeconomic status were removed, However, the underlying reason why high 2D:4D should be correlated to early MI is not known. One possibility is that markers of inflammation, such as IL-6, could be linked to both high 2D:4D and to cardiovascular risk. However, IL-6 appears to be associated with high 2D:4D in females only [14]. Here the relationship between 2D:4D and cardiovascular disease is further explored by considering their associations with the positive acute-phase reactant protein fibrinogen which is associated with major trauma such as MI. In pathological conditions, e.g. MI, the concentration of fibrinogen increases several-fold. Importantly however, even before an MI, increased fibrinogen is considered an indicator for a pro-inflammatory state and a high-risk marker for developing atherosclerosis [15–17].

Since the report by Manning and Bundred in 2001 [13], significant associations between high 2D:4D and early MI have been described in three studies of Chinese men [18–20] with one study of Chinese men reporting a non-significant relationship [21]. In addition, high 2D:4D in MI patients relative to healthy controls has been described in four studies of Chinese men [18–21] and one report of Greek men [22] with one study of Turkish men reporting a non-significant difference [23]. Overall then in White and East-Asian men there is some support for a

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negative relationship between 2D:4D and age at presentation of MI and a higher 2D:4D in MI patients compared to healthy controls.

A link between high 2D:4D and early age at MI in men suggests that atherosclerotic plaque development is more pronounced in young men with high 2D:4D than young men with low 2D:4D. A study of young (mean age 21 SD 3 years) Turkish men at autopsy has found that grade 3 (the highest development of plaque) subjects had higher mean 2D:4D than grades 1 or 2 [24].

This finding suggests two possibilities, that high 2D:4D is associated with high blood lipid levels and/or high levels of inflammation associated with vascular repair. With regard to the former, there is some evidence that the size of the fat depot in the neck is positively related to 2D:4D after the influence of BMI is removed [25]. However, the relationship between neck circumference and obesity appears to be rather complex and needs further clarification [26]. With regard to the latter, MI is associated with an elevation of acute-phase reactant proteins such as fibrinogen. Increases in fibrinogen leads to increases in plasma viscosity and aggregation of red cells and an increase in whole blood viscosity distal to the athero-thrombotic stenosis or occlusions [27]. Meta analyses of plasma fibrinogen studies have yielded a risk ratio of 1.8 which is comparable to that cholesterol and smokers versus never smokers [28–30].

Therefore, the purpose of this report was to consider the relationship between 2D:4D (right, left and Dr-l) and blood levels of fibrinogen in men who have experienced an MI and in age- and sex-matched controls who have not. Also the relationships between 2D:4D and age at presentation of MI and the differences between patients and controls in 2D:4D and fibrinogen levels were considered. Our main hypothesis was that 2D:4D would be positively related to fibrinogen levels in both patients and in controls and that this would be independent of such factors as age, BMI, smoking habits and socioeconomic status. The subsidiary predictions were that 2D:4D would be negatively related to age at presentation of MI and patients would have higher 2D:4D than their age-matched controls.

2. Methods

Participants were recruited from a Cardiac Rehabilitation Centre and from general practice in the North-West of England. Controls were matched for sex and age and where possible for socioeconomic status (Townsend Scores). Matching for the latter was achieved by drawing individuals from similar geographic areas. The Townsend deprivation scores were obtained from postal codes when made available from the participants. The scores represent a composite measure of deprivation and are made up of four variables: unemployment (as a percentage of those aged 16 and over who are economically active), non-car ownership (as a percentage of all households), non-home ownership (as a percentage of all households); and household overcrowding [31]. Therefore, high scores indicate high deprivation and a score of 0 represents an area of mean values. Our sampling area had a mean that was close to overall average values with a mean of 0.37 (SD 4.06) and a minimum of −5 and maximum of +13. With regard to ethnicity we did not restrict recruitment to one particular group. However, all the participants were White. The protocol was agreed by the local ethics committee and all participants gave written informed consent.

Digit length was measured directly from the proximal crease to the tip of the digit using vernier callipers measuring to 0.01 mm [32]. Right hand digits were measured first, followed by left hand digits and this process was then repeated. Thus, each digit measurement was followed by the measurement of another digit. This procedure was designed to eliminate the influence of each measurement on the succeeding measurement.

A 3.5 ml venous blood sample was taken into a sodium citrate 3.2% anticoagulant tube. The tube was centrifuged at 3000 rpm for 10 min

prior to analysis on the Sysmex CS2500 (CS) automated coagulation analyser. A Clauss fibrinogen measure was determined based on measuring the clotting time of diluted plasma after the addition of thrombin [33]. The clotting time obtained in this manner was then compared with that of a standard fibrinogen preparation. The Reference Range was 2.0–4.0 g/l.

We calculated repeatabilities or intra-class correlations (ICC's) of our repeated measures of 2D:4D by using Model II single factor ANOVA's. This gave us both F values (groups MS/error MS) and ICC's. The relationships between variables were examined with simple linear regression analysis and multiple regression analysis. All values of p were reported as two-tailed and $p < .05$ was considered statistically significant.

3. Results

3.1. Repeatability of 2D:4D

We calculated ICC's and F values for right 2D:4D, left 2D:4D and Dr-l. For right 2D:4D ($n = 428$) the ICC was 0.983 with a ratio of between-individual differences and error of $F = 117.60$, $p < .0001$. Left 2D:4D ($n = 431$) had an ICC of 0.975 and an F ratio of 77.99, $p < .0001$. As expected the ICC for Dr-l was lower than that of right or left 2D:4D, nevertheless it was highly significant ($n = 419$, ICC = 0.936, $F = 30.05$, $p < .0001$). Therefore the between-individual differences in right 2D:4D, left 2D:4D and Dr-l were significantly greater than error in their measurement. We calculated means for right 2D:4D, left 2D:4D and Dr-l and used these in all subsequent analyses (Table 1).

3.2. 2D:4D and age at MI

3.2.1. Descriptive statistics

There were 301 men who had experienced a myocardial infarction (MI). The mean age (SD) at MI was 60(10) years and their age at measurement was 64(10) years. With regard to 2D:4D, the means were: right 2D:4D, $n = 292$, 0.967(0.035), left 2D:4D $n = 294$, 0.965(0.034), Dr-l, $n = 285$, 0.002 (0.029). The means for height ($n = 296$), weight ($n = 300$) and BMI ($n = 295$) were 174 (7) cm, 80 (13) kg, and 26(4) respectively. At MI 55.6% ($n = 158$) of the participants smoked and 44.37% ($n = 126$) did not. The mean for Townsend scores was $n = 253$, 0.636 (4.13).

Table 1
Multiple regression analyses with age at MI as the dependent variable and independent variables: (A) right 2D:4D, BMI, Townsend Index, Smoking at MI (Y/N), $n = 229$; (B) left 2D:4D, BMI, Townsend Index, Smoking at MI (Y/N), $n = 230$; (C) right 2D:4D - left 2D:4D (Dr-l), BMI, Townsend Index, Smoking at MI (Y/N), $n = 223$.

Variable	Coefficient	St. error	St. coeff. b	t-Value	Probability
(A) Right 2D:4D $n = 229$ $r = 0.38$					
R2D:4D	−69.96	19.39	−0.23	3.61	0.0004
BMI	−0.624	0.18	−0.22	3.49	0.0006
Townsend	−0.449	0.16	−0.18	2.84	0.005
Smoking Y/N	1.745	1.30	0.084	1.34	0.18
(B) Left 2D:4D $n = 230$ $r = 0.32$					
L2D:4D	−29.23	19.76	−0.09	1.48	0.14
BMI	−0.68	0.19	−0.23	3.64	0.0003
Townsend	−0.39	0.16	−0.16	2.44	0.015
Smoking Y/N	2.403	1.32	0.12	1.83	0.07
(C) Right-Left 2D:4D $n = 223$ $r = 0.35$					
Dr-l	−51.60	25.14	−0.14	2.05	0.04
BMI	−0.70	0.188	−0.24	3.69	0.003
Townsend	−0.50	0.16	−0.20	3.07	0.002
Smoking Y/N	2.01	1.35	0.096	1.48	0.14

3.2.2. Simple linear regressions with age at MI

3.2.2.1. Digit ratio There was a weak negative relationship between right 2D:4D and age at MI ($n = 292$, $r = -0.201$, $p = .0006$, Fig. 1), but left 2D:4D was not related to age at MI ($n = 294$, $r = -0.05$, $p = .38$). The difference between right and left 2D:4D (Dr-l) was also weakly negatively related to age at first MI ($n = 285$, $r = -0.16$, $p = .005$).

3.2.2.2. BMI Men who had low BMI experienced an MI later in life than men with high BMI ($n = 295$, $r = -0.26$, $p < .0001$).

3.2.2.3. Smoking Men who smoked were younger at MI (58.80[10.48] years) than men who did not smoke (61.17 [9.73] years), $t = 1.95$, $p = .05$).

3.2.2.4. Townsend Index There was a weak negative association between Townsend scores and age at MI ($n = 253$, $r = -0.15$, $p = .02$), i.e. men living in deprived areas had their MI earlier than men in higher socio-economic circumstances.

3.2.3. Multiple regressions

Multiple regression analyses were performed with age at MI as the dependent variable and independent variables right 2D:4D (or Dr-l), BMI, Townsend Scores and smoking habits. Right 2D:4D ($b = -0.23$, $p = <0.0004$) and Dr-l ($b = -14$, $p = .04$) remained weakly negatively related to age at MI after the influence of BMI, smoking and Townsend scores was removed (Fig. 2 shows multiple regression Ta-
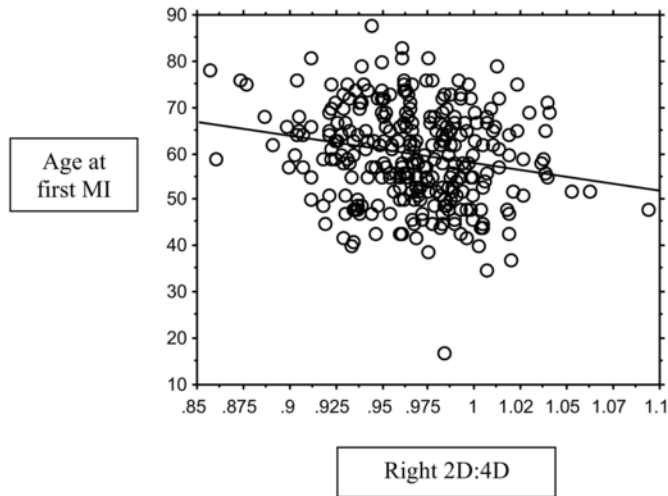

Fig. 1. The relationship between right 2D:4D and Age at First Myocardial Infarction (MI).
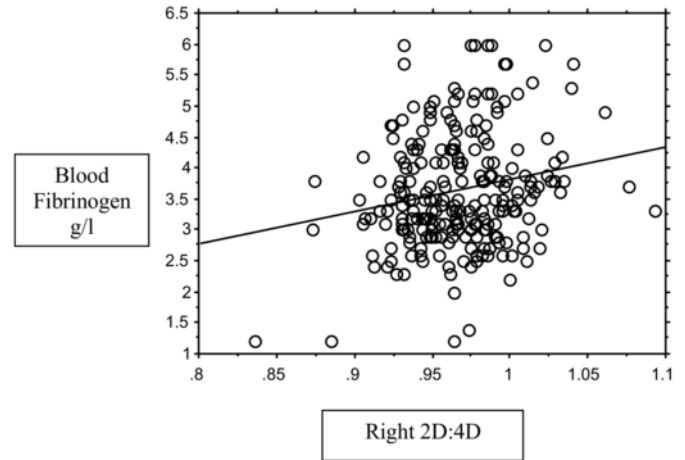

Fig. 2. Association between right 2D:4D and blood fibrinogen levels in 236 men.

bles). BMI and Townsend scores were also independent negative predictors of age at MI but smoking history and age at MI was not.

3.3. Participants who had experienced an MI and their age-matched controls

3.3.1. Descriptive statistics

There were 290 men of whom 150 had experienced an MI and 140 controls matched for age who had not experienced a heart attack. Means (SD) for age, Townsend scores, height, weight, BMI, digit length, 2D:4D (right, left, Dr-l), Fibrinogen, cholesterol (total, HDL, LDL, Chol/HDL) are given in Table 2. Participant numbers varied across traits because it was not possible to measure all participants for some of the variables. The MI and control groups did not differ in age, weight, BMI, right and left 2D:4D, or fibrinogen. There were weak differences in height and Dr-l (controls > MI's in both) Townsend scores (better socioeconomic status in controls), and digit length (controls had longer digits).

3.4. Simple linear regressions with fibrinogen

With regard to 2D:4D, there were weak positive associations between right 2D:4D and fibrinogen in the controls ($p = .02$) and in the total sample (right hand $p = .002$, see Fig. 2, and left hand $p = .009$: see Table 3). There were also weak positive associations between fibrinogen and age (MI group) and weight and BMI in the control group.

Table 2

Means and SD's in the myocardial infarction sample and age-matched controls for the following variables: Age, Townsend Scores, height, weight, BMI, digit length (2D + 4D) for the right and left hands, right 2D:4D, left 2D:4D, Dr-l and fibrinogen.

Trait	Myocardial Infarction			Controls				
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*t*	*p*
Age yr	150	65	9	140	66	7	0.76	0.45
Townsend	147	1.10	4.37	127	−0.10	4.18	2.32	0.02
Height cm	150	174	7	137	175	6	1.96	0.05
Weight kg	150	79	12	137	79	12	0.43	0.67
BMI	150	26.02	3.64	137	25.75	3.33	0.66	0.51
R Digit L mm	142	76.45	4.33	135	77.68	4.39	2.36	0.02
L Digit L mm	148	76.89	4.29	134	77.91	4.22	2.00	0.046
R2D:4D	142	0.967	0.033	135	0.967	0.037	0.003	0.998
L2D:4D	144	0.972	0.033	133	0.967	0.035	1.14	0.25
Dr-l	141	−0.004	0.018	132	0.0004	0.023	1.97	0.05
Fibrinogen g/l	131	3.65	0.86	111	3.61	1.03	0.38	0.70

Table 3

Relationships (product-moment correlations) between blood fibrinogen levels and age, Townsend scores, height, weight, BMI, mean digit lengths of the right and left hands, right 2D:4D, left 2D:4D, and Dr-l. The correlations are given for the myocardial infarction sample, the age-matched controls and the total sample.

Trait	Myocardial infarction			Control			All		
	n	r	p	n	r	p	n	r	p
Age	126	0.18	0.05	101	−0.053	0.60	227	0.077	0.25
Townsend	124	−0.10	0.27	94	−0.049	0.64	218	−0.063	0.35
Height	126	−0.059	0.51	101	0.034	0.74	227	−0.022	0.75
Weight	126	−0.045	0.62	101	0.20	0.04	227	0.069	0.30
BMI	126	−0.006	0.94	101	0.23	0.02	227	0.10	0.13
Digit L	117	−0.097	0.30	98	−0.11	0.29	215	−0.105	0.12
R2D:4D	118	0.18	0.06	100	0.24	0.02	218	0.21	0.002
L2D:4D	120	0.17	0.06	99	0.17	0.08	219	0.18	0.009
Dr-l	117	0.001	0.99	98	0.17	0.10	215	0.09	0.19

3.5. Multiple regressions with fibrinogen

Multiple regressions with dependent variable fibrinogen were carried out with independent variables right or left hand 2D:4D, age, BMI, smoking habits (yes = 1, no = 2), MI (yes = 1, no = 2), and Townsend scores (see Table 4). Digit ratio (right and left 2D:4D) remained weak positive correlates of fibrinogen (right 2D:4D $p = .01$, left 2D:4D $p = .03$). Age also remained positively related to fibrinogen levels (see Table 4).

4. Discussion

With regard to fibrinogen, we have found no differences in means for patients (3.6 [SD 0.86] g/l) versus controls (3.61 [SD 1.03] g/l) and most levels were within the reference range of 1.5 to 4.0 g/l. Cardiac rehabilitation involves aerobic exercise and regular exercise reduces fibrinogen levels [34]. Therefore, the lack of a difference may reflect a reduction in patient fibrinogen levels post MI. However, we did find evidence that 2D:4D was positively related to fibrinogen in the controls and in the total sample after controlling for a number of variables that are independent correlates of MI.

In our sample of men who have experienced an MI, we found age at MI was negatively related to 2D:4D (right and Dr-l), BMI, smoking and socioeconomic status. Right 2D:4D, Dr-l, BMI and socioeconomic status

Table 4

Multiple regressions with dependent variable blood fibrinogen levels and independent variables: 2D:4D (right or left hands), Age, BMI, smoking habits (yes = 1, no = 2), MI (yes = 1, no = 2), Townsend score.

Variable	Coefficient	Std. error	Std. coeff.	t	p
Right 2D:4D	4.62	1.801	0.176	2.566	0.011
Age	0.019	0.008	0.182	2.489	0.014
BMI	0.032	0.018	0.123	1.748	0.082
Smoke Yes = 1	−0.066	1.972	1.653	0.449	0.654
MI Yes = 1	−0.143	0.126	−0.079	1.132	0.259
Townsend Score	−0.009	0.015	−0.046	0.651	0.516

Variable	Coefficient	Std. error	Std. coeff.	t	p
Left 2D:4D	4.232	1.892	0.153	2.236	0.026
Age	0.017	0.008	0.166	2.269	0.024
BMI	0.028	0.019	0.106	1.49	0.138
Smoke Yes = 1	−0.036	0.151	−0.017	0.237	0.813
MI Yes = 1	−0.184	1.972	1.653	1.438	0.152
Townsend Score	−0.016	0.015	−0.075	1.071	0.286

remained significant after multiple regression analysis but significance was lost for smoking habits. With regard to 2D:4D, our findings replicated three earlier reports on East-Asian men [18–20] and provided support for one of our predictions. However, the comparisons between the MI group and age-matched controls found no differences for 2D:4D, weight, BMI, or fibrinogen, and weak differences for height, Dr-l, socioeconomic status and digit lengths (all greater for controls). The null findings for 2D:4D did not replicate four earlier reports from White and East-Asian men [18–21].

Overall, we think our results suggest that high 2D:4D is a correlate of elevated fibrinogen levels and early MI. However, we are unable to explain why the MI group and controls did not differ for mean 2D:4D as in a number of studies. It should be noted that our findings for MI may also have relevance for other diseases that are related to elevated fibrinogen levels, these include; stroke, Alzeimers disease, rheumatoid arthritis and multiple sclerosis [15]. With regard to ischemic stroke, in comparison to healthy controls, male stroke patients have low levels of testosterone [30] and high 2D:4D [35]. This replicates the relationships between MI patients and their healthy controls. There has been little in the way of large studies of digit ratios for the remaining diseases.

In addition to associations between disease and the 2D:4D/fibrinogen correlation there may also be implications for associations between 2D:4D and performance in sport. There is a robust negative correlation between 2D:4D and performance in many sports [36]. However, the effect size varies across sports such that closed disciplines that place emphasis on endurance, such as distance running, show greater effect sizes than those that require strength and/or open interaction with other participants [37,38]. This pattern may, in part, reflect a positive correlation between 2D:4D and blood levels of fibrinogen. The viscosity of blood is dependent on sex such that men have greater viscosity than women over the period from adolescence to middle-age. Fibrinogen is a large molecule which accounts for > 20% of the total viscosity and at higher levels fibrinogen may interact with the concentration of erythrocytes which accounts for greater 25% of viscosity [39]. The rheological properties of blood may be an important factor in endurance events as the heart must work hard to overcome the resistance of the vascular system. In such disciplines men who have low fibrinogen levels, i.e. athletes with low "masculinised" 2D:4D, may be at an advantage over those who have high fibrinogen, i.e. athletes with high "feminized" 2D:4D.

In conclusion, we have found a significant positive correlation between 2D:4D and blood fibrinogen levels in a sample of men consisting of those who have experienced an MI and their age-matched controls. Levels of blood fibrinogen are a predictor of MI and it was found that 2D:4D was negatively correlated with age at MI, although we were unable to show a difference in 2D:4D between the MI group and controls. The positive correlation between 2D:4D and fibrinogen may, in part, explain a relationship between high 2D:4D and coronary heart disease in men. We also discuss the possibility that the relationship between

2D:4D and fibrinogen may be relevant to associations between 2D:4D and diseases such as ischemic stroke, Alzheimers disease, rheumatoid arthritis, and multiple sclerosis. In addition it is further suggested that the strong negative correlation between 2D:4D and endurance sports may be moderated by a positive association between 2D:4D and fibrinogen.

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Conflict of interest statement

None declared.

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