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Hemostatic factors in Australian Aboriginal and Torres Strait Islander populations

Zaimin Wang[a,b], Kevin Rowley[a,c,*], James Best[a], Robyn McDermott[d], Michael Taylor[e], Kerin O'Dea[a,f,g]

[a]*Department of Medicine, St Vincent's Hospital, The University of Melbourne, Melbourne, VIC 3065, Australia*
[b]*Centre for Chronic Disease, School of Medicine, The University of Queensland, Brisbane, QLD 4029, Australia*
[c]*Onemda VicHealth Koori Health Unit, Centre for Health and Society, School of Population Health, The University of Melbourne, VIC 3010, Australia*
[d]*Health Science Division, University of South Australia, Adelaide, SA 5001, Australia*
[e]*St Vincent's Pathology, St Vincent's Hospital, Melbourne, VIC 3065, Australia*
[f]*Menzies School of Health Research, Darwin, NT 0811, Australia*
[g]*Institute of Advanced Studies, Charles Darwin University, Darwin, NT 0909, Australia*

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Abstract

Hemostatic processes are important in precipitating myocardial infarction and stroke. Elevated plasma fibrinogen is considered a risk factor for cardiovascular diseases (CVDs), but the results of previous studies on the association of plasma factor VIIc activity with CVD and diabetes have been inconsistent. The aim of the present study was to explore the association of plasma fibrinogen and factor VIIc to clinical characteristics and estimated coronary heart disease (CHD) risk in Aboriginal and Torres Strait Islander peoples. Cross-sectional surveys of Australian Aboriginal people (n = 852) and Torres Strait Islanders (n = 276) aged 15 years and older were conducted from 1993 to 1995. Anthropometric characteristics, blood pressure, fasting plasma fibrinogen, factor VIIc, total and high-density lipoprotein cholesterol, triglycerides, and glucose were measured. Levels of fibrinogen (mean, 95% confidence interval) for Aboriginal (3.52, 3.44-3.59 g/L) and Torres Strait Islander people (3.62, 3.49-3.75 g/L) were higher compared with previous reports from other populations. Factor VIIc (mean, 95% confidence interval) was especially high in Torres Strait Islanders (116%, 111%-122%) compared with Aboriginal people (99%, 97%-102%). Fibrinogen increased with age in both ethnic groups and sexes. Fibrinogen was independently associated with female sex, body mass index, renal dysfunction, low levels of high-density lipoprotein cholesterol and diabetes, whereas the independent predictors for factor VIIc were Torres Strait Islander ethnicity, female sex, body mass index, renal dysfunction, and total cholesterol. Average fibrinogen levels were high (>3.5 mg/dL) even for people considered "below average risk of coronary heart disease" according to conventional risk factor levels. For Aboriginal women, levels of fibrinogen and factor VIIc were significantly higher for persons at high risk than those at below average risk. The data suggest that plasma fibrinogen and factor VIIc might be important factors mediating the elevated CVD in Australian Indigenous Peoples. These data may have implications for prevention and treatment of CVD in Australian Indigenous communities.

1. Introduction

Hemostatic processes are important in precipitating cardiovascular disease (CVD) events, such as myocardial infarction and stroke. Elevated plasma fibrinogen has been considered a risk factor for CVDs since the early 1980s [1-6]. In recent years, a growing number of studies have focused on fibrinogen in diabetes, and there is evidence that fibrinogen is a strong predictor of atherosclerotic CVD in diabetes. Thus, fibrinogen has been included in the "cardiovascular risk profile" of diabetes patients [7,8]. In contrast, despite some exceptions supporting an association of factor VII to CVD risk [9-14], some epidemiologic studies and genetic polymorphism data suggested no association between plasma factor VIIc activity and CVD nor with diabetes [5,6,15]. Cigarette smoking was found to be related to plasma fibrinogen level [3,12,16], which may explain part of the association between smoking and CVD.

There have been few studies on the relation of fibrinogen and factor VIIc with multiple metabolic abnormalities in

* Corresponding author. Department of Medicine, St Vincent's Hospital, The University of Melbourne, Melbourne, VIC 3065, Australia. Tel.: +61 3 8344 0814; fax: +61 3 8344 0824.
E-mail address: rowleyk@unimelb.edu.au (K. Rowley).

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healthy populations, but several reports indicate that there could be an association [17]. Like insulin resistance, fibrinogen is inversely related to socioeconomic status [18]. It is also considered important in the acute-phase inflammatory response [13,19,20], aspects of which have been linked with central adiposity. Factor VIIc is reported in some but not all studies to be related to dietary saturated fat intake, body mass index (BMI), waist-hip ratio, and insulin resistance [10,14,21-23].

Australian Aboriginal and Torres Strait Islander peoples experience high cardiovascular mortality, high prevalence of smoking and conditions associated with insulin resistance, generally low socioeconomic status, poor dietary quality, and a high inflammatory load [24-28]. Conventional algorithms for calculating risk of coronary heart disease (CHD) substantially underestimate risk for Aboriginal people [29], and elevation of hemostatic factors may contribute to this phenomenon by increasing the risk of acute events. The aim of the present study was to explore the association of plasma fibrinogen and factor VIIc to clinical characteristics and estimated CHD risk in Aboriginal and Torres Strait Islander peoples.

2. Materials and methods

2.1. Participants

Between 1993 and 1995, 11 communities in Cape York, Torres Strait, and Central Australia were screened for diabetes and other cardiovascular risk factors. Participation was voluntary and open to all community members aged 15 years or older. Response rates ranged from 40% to 86%. The survey sample was representative of the national Indigenous population with respect to age and sex distribution [26]. Ethnicity was determined by self-report. After excluding non-Indigenous people, 852 Aboriginal people and 276 Torres Strait Islanders aged 15 years and older were included in the present analysis. The age of subjects ranged from 15 to 94 years (mean, 36 years) and 72% of the subjects were younger than 45 years. Further details of screening procedures have been reported elsewhere [30-32].

The study was approved by Deakin University Ethics Committee, the Alice Springs Institutional Ethics Committee, the Ethics Committee of the Peninsula and Torres Strait Regional Health Authority, and Cairns Base Hospital Institutional Ethics Committee and conducted with support from relevant Indigenous community organizations.

2.2. Biochemical analyses

Plasma fibrinogen was estimated by using a modified Ratnoff and Menzie method [33] on an ACL 2000 (Beckman-Coulter, Fullerton CA). Calibration was achieved using commercial standards (Behring, Marurg, Germany). Accuracy and linearity were checked by assaying a sample of known fibrinogen concentration (independently determined as 4.8 g/L) at a series of 7 dilutions from 1.0 to 0.125. Mean fibrinogen content based on these assays was 4.8 g/L (coefficient of variation [CV], 6.4%), indicating good external validity and linearity of the assay. The manufacturer of the reagents guarantees linearity of the method from 0.6 to 6.0 g/L. Study samples were run undiluted and at ½ dilution and results were accepted when 2 estimates were within 10% of each other. Quality control samples were included in every run, with CVs of 13.7% at 1 mg/L and 8.6% at 2.7 mg/L. Factor VII coagulant activity (factor VIIc) was assayed with an ACL 100 automated coagulation laboratory analyzer (Beckman-Coulter) with factor VII–deficient plasma and rabbit thromboplastin as reagents. Coefficient of variation for a quality control sample (Instrumentation Laboratory, Lexington, MA; reference range, 67%-107%) included in every run was 8% (mean, 89%). In a volunteer sample of non-Indigenous postmenopausal women (n = 102; age range, 45-74 years) for whom fibrinogen and factor VII were assayed by us using the same instruments and methods, mean (SD) for fibrinogen was 3.3 (0.5) g/L (R. M. Stoney, unpublished data, 1997), and mean (SD) factor VII was 115% (26%) and 104% (26%) for diabetic and nondiabetic persons, respectively [34].

Plasma glucose, triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by using standard enzymatic techniques (Boehringer-Manheim reagents; interassay CV, <7%). Insulin was measured by radioimmunoassay using a specific antibody (Linco Research, St Charles, MO; interassay CV, 9%-13%). Insulin resistance was calculated by using the homeostasis model assessment (HOMA) formula [35]. Urinary albumin concentration was measured by using immunonephelometry (Kallestadt QM 300 [Chaska, MN] or Beckman 360 Array [Fullerton, CA] nephelometers; interassay CV, 3%-5%). Urinary creatinine concentration was measured by using an alkaline picrate method (Olympus AU800 Autoanalyzer, Tokyo, Japan; interassay CV 2%). According to the albumin-creatinine ratio (ACR), renal function was categorized into normal (ACR < 3.4 mg/mmol), microalbuminuria (ACR, 3.4-33.9 mg/mmol), and macroalbuminuria (ACR ≥ 34 mg/mmol).

2.3. Anthropometric measurements and blood pressure

Body weight was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm, and waist and hip circumferences to 0.1 cm, using standard techniques. Sitting blood pressure was measured with the subjects seated at least 5 minutes before measurement with a Dinamap automated blood pressure monitor (Critikon; Tampa, FL). The mean of 3 consecutive readings was taken.

Diabetes was defined as fasting plasma glucose of 7.0 mmol/L or greater, 2-hour postglucose load of 11.1 mmol/L or greater, or use of antidiabetic medication [36]. Abdominal obesity was defined as waist girth greater than 102 cm in men or greater than 88 cm in women [37]. Participants were defined as being a smoker and drinking alcohol if they answered "yes" to the questions "Do you currently smoke?" and "Do you currently drink alcohol?," respectively, in the self-reported

Table 1
Clinical characteristics of Aboriginal and Torres Strait Islander populations

	Aboriginal people			Torres Strait Islanders		
	Men (n = 368)	Women (n = 484)	*P*	Men (n = 128)	Women (n = 148)	*P*
Age (y)	34 ± 16	36 ± 15	.076	36 ± 16	38 ± 15	.432
BMI (kg/m^2)	26.0 (25.4-26.7)	27.5 (26.9-28.1)	.001	29.6 (28.5-30.7)	31.1 (30.1-32.2)	.038
WHR	0.92 (0.91-0.93)	0.86 (0.85-0.87)	<.001	0.93 (0.87-0.99)	0.92 (0.87-0.97)	.766
SBP (mm Hg)	135 (133-136)	124 (123-126)	<.001	134 (131-137)	125 (122-128)	<.001
DBP (mm Hg)	76 (75-77)	71 (70-72)	<.001	74 (72-76)	67 (65-69)	<.001
Total cholesterol (mmol/L)	5.17 (5.06-5.29)	4.79 (4.69-4.89)	<.001	4.78 (4.58-4.97)	4.67 (4.49-4.86)	.454
HDL cholesterol (mmol/L)	0.83 (0.81-0.85)	0.88 (0.85-0.90)	.005	1.01 (0.96-1.06)	1.0 (0.95-1.05)	.698
Triglycerides (mmol/L)	2.22 (2.10-2.35)	1.74 (1.66-1.83)	<.001	1.71 (1.53-1.91)	1.55 (1.40-1.72)	.208
Fasting insulin (μU/mL)	15.4 (14.5-16.3)	17.6 (16.7-18.5)	.001	15.0 (13.7-16.5)	18.6 (17.1-20.3)	.001
Diabetes (%)	11 (8-15)	16 (13-20)	.047	17 (11-24)	36 (28-44)	.001
Microalbuminuria (%)	20 (16-24)	24 (21-28)	.135	24 (17-32)	25 (18-32)	.890
Macroalbuminuria (%)	9 (6-12)	13 (10-16)	.098	5 (1.0-8)	15 (9-20)	.005
Smoking (%)	53 (47-58)	16 (13-20)	<.001	57 (49-66)	37 (30-45)	.002
Fibrinogen (g/L)	3.39 (3.27-3.50)	3.63 (3.54-3.73)	.001	3.45 (3.25-3.64)	3.84 (3.65-4.02)	.005
Factor VIIc (%)	96 (92-99)	104 (100-107)	.001	107 (98-116)	126 (117-136)	.005

Values are mean ± SD for age and mean (95% CI) for all other variables. Variables were adjusted by age. WHR indicates waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

questionnaire. Ten-year estimated CHD relative risk was calculated based on the Framingham scores for participants aged 30 to 74 years [38]. CHD relative risk was classified as 5 categories, ie, low risk (representing an estimated absolute risk of total CHD ranging from ≤2% in 30- to 34-year-olds to ≤8% in 70- to 74-year-olds), below average risk (2%-13%), average risk (5%-15%), moderately above average risk (6%-24%), and high risk (8% to >27%) [38]. As only 3 individuals fell into the "low-risk" category, this group was combined with the "below average risk" category.

2.4. Statistical analysis

Data analysis was undertaken using the Statistical Package for Social Sciences (SPSS) version 11.5 (SPSS, Chicago, IL). Mean levels of plasma fibrinogen and factor VIIc across categories of age, sex, ethnicity, and the linear trend with age and the 10-year CHD relative risk were examined by analysis of variance. Data were presented as mean and 95% CI for normally distributed variables, as percentage for categorical variables, or as geometric mean and 95% CI computed on the log-transformed variables and converted to the original scale of measurement for log-normally distributed variables. Stepwise multiple regression models with fibrinogen level and factor VIIc as the dependent variables were used to identify independent predictor variables. Age and sex were included in all models, and variables with $P > .10$ were excluded from final models. Statistical significance was defined at the level of $P < .05$ (2-tailed). Participants were categorized into 2 broad groups: Aboriginal people and Torres Strait Islanders. Although we recognize the diversity of cultural and social circumstances within groupings, the statistical power of the study was not sufficient to allow smaller, more precise groupings.

3. Results

Average age of participants was 34 to 38 years (Table 1), reflecting the young age of this population due to extremely

Table 2
Hemostatic factors stratified by age group, sex, and ethnicity

	Aboriginal people				Torres Strait Islanders			
	Men	*n*	Women	*n*	Men	*n*	Women	*n*
Fibrinogen (g/L)								
15-24 y	3.22 (3.03-3.41)	127	3.43 (3.24-3.61)	132	3.18 (2.87-3.50)	39	3.40 (3.09-3.71)	33
25-34 y	3.35 (3.16-3.53)	93	3.54 (3.37-3.71)	139	3.45 (2.96-3.95)	28	3.73 (3.24-4.22)	36
35-44 y	3.24 (2.93-3.54)	50	3.49 (3.29-3.69)	71	3.55 (3.17-3.93)	26	3.87 (3.49-4.25)	25
45-54 y	3.55 (3.23-3.87)	39	3.96 (3.63-4.29)	60	3.35 (2.92-3.79)	14	3.95 (3.56-4.33)	22
55+ y	3.83 (3.43-4.23)	47	4.13 (3.84-4.42)	71	3.78 (3.20-4.37)	20	4.50 (3.90-5.11)	26
$P_{\text{linear trend}}$	.002		<.001		.066		.001	
Factor VIIc (%)								
15-24 y	91 (87-95)	129	101 (94-148)	132	96 (89-103)	39	118 (96-144)	34
25-34 y	95 (88-103)	93	102 (95-109)	141	108 (87-133)	28	123 (103-148)	39
35-44 y	91 (86-97)	55	102 (95-109)	72	121 (106-139)	27	139 (107-181)	26
45-54 y	110 (98-123)	42	107 (101-113)	63	128 (101-162)	14	119 (103-139)	22
55+ y	101 (91-113)	49	112 (104-120)	76	98 (86-111)	20	137 (109-172)	26
$P_{\text{linear trend}}$	.857		.042		.201		.266	

Data are mean (95% CI), sample size.

Table 3
Multivariate regression analysis of fibrinogen (g/L) and factor VIIc (%) activity

Variable	Fibrinogen				Factor VIIc[a]			
	B	SE	*β*	*P*	*B*	SE	*β*	*P*
Age (y)	0.009	0.002	0.129	<.001	0.001	0.001	0.038	.241
Sex[b]	−0.208	0.068	−0.094	.002	−0.090	0.022	−0.126	<.001
Ethnicity[c]	–	–	–	–	0.098	0.028	0.111	.001
BMI (kg/m^2)	0.025	0.005	0.144	<.001	0.007	0.002	0.111	<.001
Albuminuria[d]	0.147	0.055	0.091	<.001	0.037	0.017	0.070	.034
HDL cholesterol (mmol/L)	−0.417	0.131	−0.097	.002				
Total cholesterol (mmol/L)[a]	–	–	–	–	0.057	0.010	0.187	<.001
Diabetes	0.275	0.098	0.096	.005	–	–	–	
R^2				*.117*				*.089*

[a] Log-transformed variables.
[b] Females coded 0, males coded 1.
[c] Aboriginal people coded 0, Torres Strait Islanders coded 1.
[d] ACR less than 3.4, 3.4 to 33, and 34 mg/mmol or greater.

high premature mortality, particularly from CVD [25-27]. Body mass index, fasting insulin, fibrinogen, factor VIIc, and prevalence of diabetes were significantly higher for women compared with men, whereas systolic and diastolic blood pressure and prevalence of smoking were higher among men (Table 1). Mean levels of fasting insulin and triglycerides and prevalence of diabetes were relatively high and HDL cholesterol low, consistent with a high degree of insulin resistance.

The difference in mean fibrinogen levels between Aboriginal and Torres Strait Islander peoples was not statistically significant (3.52 and 3.62 g/L; $P = .163$), whereas factor VIIc activities (mean, 95% CI) of Torres Strait Islanders (116%, 111%-122%) were significantly greater compared with Aboriginal people (99%, 97%-102%; $P < .001$). Fibrinogen significantly increased with age in all Aboriginal people and Torres Strait Islander women (Table 2). There was significant correlation between fibrinogen and insulin resistance in Aboriginal people ($r = 0.11$, $P = .004$) but not in Torres Strait Islanders (data not shown). There was a significant linear trend of factor VIIc levels with increasing age in Aboriginal women only (Table 2).

Mean fibrinogen concentrations and factor VIIc activities were significantly higher in the presence of diabetes, abdominal obesity, and micro- and macroalbuminuria in both ethnic groups, but fibrinogen and factor VIIc did not vary by categories of smoking and drinking alcohol (data not shown). Multiple regression analysis of fibrinogen concentration showed independent associations with age, high BMI, low HDL cholesterol, diabetes, female sex, and renal dysfunction (Table 3). Similarly, there were significant independent associations of factor VIIc activity with higher total cholesterol, female sex, Torres Strait Islander ethnicity, high BMI, and renal dysfunction (Table 3).

The relationship of hemostatic factors to conventional risk factors was further examined by categorizing participants aged 30 to 74 years into CHD risk strata based on the Framingham risk algorithm [38]. Among Aboriginal people, fibrinogen ($P = .017$) and factor VIIc levels ($P = .003$) increased significantly with increasing estimated CHD risk, whereas these associations were close to significant in Torres Strait Islander people ($P = .070$ for fibrinogen and $P = .084$ for factor VIIc) (Fig. 1). There were no significant interactions between gender and the estimated CHD risk. The mean fibrinogen level and factor VIIc activity (mean, 95% CI) were 3.5 g/L (3.30-3.61 g/L) and 102% (98%-107%) in people otherwise estimated to be at below average CHD risk.

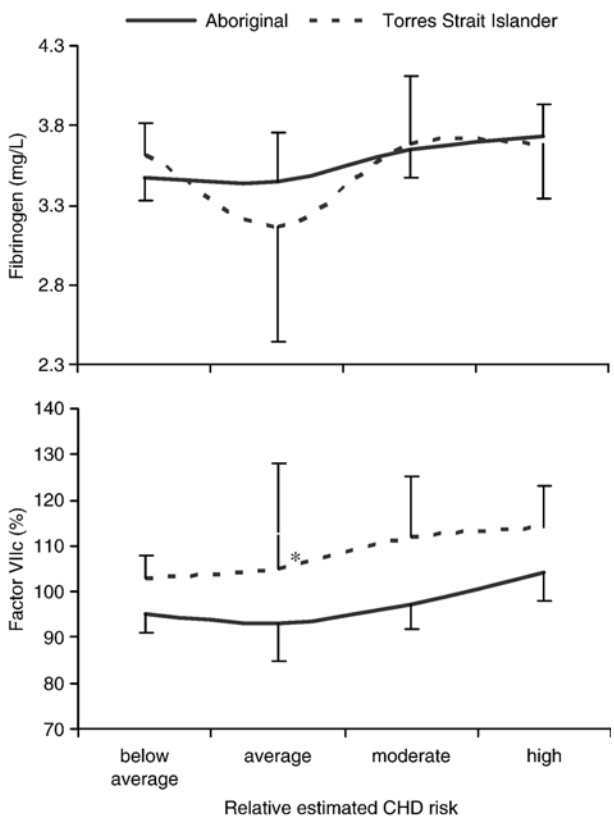

Fig. 1. Association between hemostatic factors and estimated CHD risk for persons aged 30 to 74 years. Data are mean for fibrinogen and geometric mean for factor VIIc. Error bars are 95% CI. *Excludes 3 outlying values greater than 350%.

4. Discussion

The 2 most striking observations in this study are first, that these 2 populations of Indigenous Australians have higher fibrinogen levels than average levels reported for other populations, and second, that Torres Strait Islanders have much higher factor VIIc levels than Aboriginal people. The generally high fibrinogen levels are consistent with the higher morbidity and mortality from CVD and diabetes among Indigenous people. Fibrinogen was elevated in both ethnic groups. In a community-based survey sample of non-Indigenous Australian women aged 45 to 74 years, drawn from the Melbourne Collaborative Cohort Study and with samples assayed in the same laboratory, average fibrinogen was 3.3 g/L (R. M. Stoney, unpublished data, 1997). In the present study, mean fibrinogen for Indigenous people in this age range was 3.9 g/L. Mean values for fibrinogen reported for other healthy populations range from 2.2 to 3.7g/L [9,10,39,40]. Fibrinogen concentrations greater than 3.43 g/L were associated with a 2-fold increased risk of myocardial infarction in a US population aged 40 to 84 years compared with those with fibrinogen less than 3.43 g/L [4], whereas some other previous studies demonstrated a clear increase in CHD risk at fibrinogen concentrations between 3.3 and 3.7 g/L [2]. In the present study, nearly 50% of people had fibrinogen levels of 3.5 g/L or higher, including the group of people at below average risk of CHD according to conventional risk factor levels. Diabetes, albuminuria, and HDL cholesterol were associated with fibrinogen level, consistent with previous studies [17,41,42]. Although cross-sectional findings, should not be taken as causal, the evidence that fibrinogen was related to higher BMI, renal function, and diabetes in this present study would have implications for the prevention of CHD. Other studies have reported higher fibrinogen levels in smokers [3,12,16]. The possible reasons for the lack of the expected association with smoking in the present study could be due to the definition of smoking, which did not consider the duration and dose-response effect. Some previous studies found that insulin resistance was related to higher fibrinogen levels [43], consistent with the finding in Aboriginal people in the present study, and glitazone treatment, which improves insulin sensitivity, also reduces fibrinogen [44]. Good glycemic control also favorably influenced fibrinogen concentrations in diabetic patients in whom basal fibrinogen concentrations were increased [8].

By comparison, previous population-based and opportunistic studies reported that factor VIIc activity values range from 93% to 116% [9,10,39,40], which were similar to those values reported here for Aboriginal people but generally lower than observed for Torres Strait Islanders. For the survey sample of non-Indigenous women (aged 45-74 years) cited above, mean factor VIIc activity was 104% and 115% for nondiabetic and diabetic participants, respectively [34], compared with 116% for Aboriginal people and 137% for Torres Strait Islanders in this age range. There was a significant linear trend of factor VIIc with increasing age in Aboriginal women but not in other subgroups. BMI, renal function, and total cholesterol were independently associated with factor VIIc in Aboriginal and Torres Strait Islander people. Torres Strait Islanders had significantly higher factor VIIc activity independently of these other variables.

Multiple regression analyses using anthropometry, metabolic characteristics, and smoking and drinking alcohol as predictors could account for only 12% of variance in fibrinogen concentrations and only 9% of variance in factor VIIc, similar to other published studies [45-48]. Besides possible genetic differences between Australian Indigenous people and other ethnicities, other factors contributing to elevated hemostatic factors and the apparent variation between populations in this study may include dietary factors, physical activity levels [19,49], and other determinants yet to be identified. A number of previous studies suggested that factor VIIc was associated positively with fat and protein intake [14,22,23,50]. The present observation that factor VIIc was independently associated with plasma cholesterol, particularly for Torres Strait Islanders, is consistent with an effect of higher dietary saturated fat [14,22], and anecdotal evidence suggests very high fat diets are common in Torres Strait Islander communities. Plasma cholesterol levels were higher in Torres Strait Islanders compared with Aboriginal people in these communities [32,33], which may partly account for the higher mean factor VIIc in the former group, but some ethnic difference remained after adjustment for plasma cholesterol in regression analysis. An as yet unexplained genetic influence cannot be excluded, nor can social environmental influences [18] on factor VIIc activity, and the same may apply to determinants of fibrinogen concentration. We note, however, that a recent study of the Framingham population identified only a modest contribution of common genetic variants to circulating levels of hemostatic factors (from 1% to 10% of variation in fibrinogen and factor VIIc, respectively [51]).

The association between inflammation and hemostatic factors is worth examination, as inflammation is an important mechanism in CVD, and inflammation influences plasma fibrinogen concentrations [5,20]. As an acute-phase inflammatory protein, fibrinogen may play an important role in precipitating thrombosis, which is an important mechanism in acute myocardial infarction [52]. Previous studies suggested that fish-rich diets may decrease the risk for CVDs through the modulation of plasma lipids, fibrinolytic activities, or inflammatory markers [53-55]. In our study, no information on individual dietary patterns or C-reactive protein, a nonspecific inflammatory maker known to predict CVD, was available in the present data set for further analysis. However, plasma C-reactive protein concentration was reported to be very high in several other Aboriginal communities [28,56].

The Framingham CHD risk algorithm was shown to underestimate by at least 3-fold the risk of CHD in an Aboriginal population in the Northern Territory [29]. In the

present populations, levels of fibrinogen and factor VIIc were modestly associated with increasing estimated risk of CHD, but average fibrinogen concentrations were still relatively high even in people apparently at below average CHD risk, suggesting that hemostatic factors may partly mediate the excess risk not accounted for by conventional factors. The observations may have important implications for clinical management of CVD risk. In addition to the potentially beneficial effects of insulin sensitivity and good glycemic control listed above, use of aspirin is recommended for Aboriginal and Torres Strait Islander people with diabetes and/or multiple CVD risk factors [57]. However, use of aspirin or other antithrombotic agents is not part of routine clinical audits for patients with these conditions; the elevations of hemostatic factors reported here suggest more attention should be given to this aspect of care.

In conclusion, we have shown high levels of circulating fibrinogen in Aboriginal and Torres Strait Islander populations and high factor VIIc activity among Torres Strait Islanders. The elevations of hemostatic factors are only partly explained by associations with conventional CVD risk factors and, therefore, they might be important factors mediating the elevated risk of CVD in these populations. These data may have implications for prevention and treatment of CVD in Australian Indigenous communities.

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