Plasma fibrinogen and its correlates in adult Saudi population

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ABSTRACT

Objective: To determine plasma fibrinogen and its correlates in the adult Saudi population and to investigate hyperfibrinogenemia as a possible risk factor for cardiovascular diseases (CVD).

Methods: A cross-sectional survey was designed and carried out through multi-stage stratified cluster random sampling of every third house in 6 heterogeneously populated districts of Riyadh, Kingdom of Saudi Arabia, during the period 1999 to 2002. Demographic and clinical data of 2263 adult Saudi subjects, consisting of 1934 (85.5%) men and 329 (14.5%) women, was collected through a standard questionnaire. Body mass index (BMI), blood pressure (BP) and history of smoking were recorded. Plasma fibrinogen, total serum cholesterol, triglycerides, high density lipoproteins (HDL) and blood sugar were determined in fasting blood samples.

Results: The majority (84.6%) of the subjects were between 20-50 years of age. The mean plasma fibrinogen was 336 ± 115 mg/dl, and was increasing with age both in men and women. The mean ± SD fibrinogen in women (357 ± 118 mg/dl) was significantly higher (*p* value of 0.03) than men (332 ± 114 mg/dl). Hyperfibrinogenemia (>400 mg/dl) was indicated in 554 (24.6%) of the total subjects. Among hyperfibrinogenemic Saudi adults, the prevalence of hypercholesterolemia was 14.3%, hypertriglyceridemia 24%, obesity 26.3%, systolic/diastolic hypertension 11.5% and 11% and hyperglycemia 26% (in women only). A reciprocal relation was observed between HDL and plasm fibrinogen. Significant positive correlation was seen between fibrinogen and BMI, systolic and diastolic BP and total cholesterol. There was no significant difference in the distribution of plasma fibrinogen between smokers and non-smokers (*p* value of 0.864). The difference in the magnitude of metabolic as well as modifiable CVD risk factors between smokers and non-smokers was not significant, except serum triglyceride which was significantly higher in smokers than non-smokers (*p* value of 0.020).

Conclusion: A significant positive correlation was observed between hyperfibrinogenemia and obesity, systolic/diastolic hypertension and hypercholesterolemia. Our results thus support the earlier reports that hyperfibrinogenemia is a potential CVD risk factor. Unlike other reports, we could not find any correlation between smoking and plasma fibrinogen in our studied subjects. The value of hyperfibrinogenemia as a definite risk factor for CVD has to be quantified in future case-control studies comparing its significance between CVD subjects and normal controls.

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Cardiovascular diseases (CVD) have emerged as a leading cause of considerable morbidity and mortality in many industrialized as well as developing countries of the world. According to the 3rd (1991-1993) monitoring report of the World Health Organization (WHO), cardiovascular

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diseases caused 12 million deaths in both industrialized and developing countries of the world each year.[1,2] Cardiovascular disease is also emerging as a major health problem in the Eastern Mediterranean Region including the Kingdom of Saudi Arabia (KSA) and neighboring Arab countries where the proportion of deaths from cardiovascular events ranges from 25-45%.[3] Rapid socioeconomic growth over the last 3 decades has resulted in the change of life pattern. Daily caloric intake has increased and so is the lack of physical activity both of which has significantly contributed to the increase in the prevalence of modifiable CVD risk factors among Saudi adults.[4] Al-Balla et al[5] studied the pattern of admission at a tertiary healthcare center over a period of 5-years and reported that CVD were among the most frequent causes of hospital admissions and bed occupation accounting for 25.9% of the total admissions. In another report, Al-Balla et al[6] showed that CVD constituted the major cause of morbidity and mortality among elderly hospitalized patients. Al-Nuaim[4] estimated the prevalence of some major CVD risk factors in 2059 Saudi subjects aged 30-64-years, and reported a high prevalence of metabolic risk factors for CVD among Saudi population. The future risk of CVD can be significantly reduced if the risk factors are precisely identified, and the preventive measures are effectively applied. All along, the research has been mainly focused on lipids, blood pressure, diabetes and smoking as the widely accepted risk factors for atherosclerosis. However, there has been growing evidence of the importance of plasma fibrinogen in the development of ischemic CVD. The fact that fibrinogen is related to CVD disease was first reported in the 1950s when its concentration was found to be elevated in patients with ischemic heart disease.[7-10] Later, Meade et al[11] while investigating the relationship of hemostatic factors to the ischemic heart disease in their Northwick Park Heart Study found out fibrinogen to be an independent risk factor for ischemic heart disease in middle-aged white men during 4-year and 10-year follow up periods.[12] Since then, substantial evidence has accumulated through several large-scale prospective epidemiological studies suggesting that raised levels of plasma fibrinogen represents a major risk for CVD and is a powerful independent predictor for myocardial infarction and stroke.[13-21] Other experimental and clinical findings suggest that fibrinogen may also be a risk factor for the sequel of atherothrombotic events.[19,22,23]

The purpose of this cross-sectional household survey was to estimate plasma fibrinogen levels and to identify its correlates among Saudi adults living in 6 heterogeneously populated districts of Riyadh, KSA. It is hoped that results obtained in this study will not only enable us to identify population sub-groups which are substantially at greater risk for ischemic heart disease, but would also advance our knowledge to design effective health education and disease prevention programs to reduce the risk of CVD in KSA. To the best of author's knowledge, this is the first epidemiological study from KSA investigating plasma fibrinogen in the presence of some CVD risk factors in Saudi adults (≥20 years).

Methods. ***Study population.*** A total of 2358 Saudi adults of both genders from 6 heterogeneously populated districts of Riyadh, KSA (population size 2.8 million as per 1998 National Census) participated in this survey. A Saudi adult was defined as any individual aged 20-years and above and holding a valid Saudi Nationality Identity Card (SNIC). The age of the participants was calculated from the officially endorsed date of birth on SNIC. The administrative map of Riyadh was obtained. The survey was designed and executed during the years 1999 to 2002 by a team of health experts, consisting of primary healthcare consultants, an epidemiologist, a female nurse and healthcare social workers. A multistage stratified cluster random sampling technique was employed for the selection of the required sample size. A systematic random sampling method of every third house was used to select the final sample of household units in the clusters selected during the second stage of the sampling process. All the adults aged 20-years and above who consented to participate in this study were included in the final sample. Since the study required collection of blood, therefore, approval was obtained from the Ethical Committee of the Ministry of Health, Riyadh, KSA. A standard questionnaire was constructed and validated. It included personal, demographic, socio-economic and medical history. Members of the survey-team were trained and oriented to conduct the fieldwork. The nature and usefulness of the study as well as the importance of filling the questionnaire properly were explained. The last part of the questionnaire included a data collection form for the documentation of blood pressure, weight and height, plasma lipids, blood sugar, plasma fibrinogen and smoking habits. Anthropometric measurements were taken using a standard portable scale. Body mass index (BMI) was calculated by the formula: weight (kg)/height $(m)^2$. Systolic and diastolic blood pressure was measured using a periodically calibrated mercury sphygmomanometer. All the measurements were made on the right arm of seated participants after a 5 minute rest and were recorded to the nearest reading. Two measurements were taken one before answering the questionnaire and the second 20-25 minutes later. The arithmetic mean of both readings was documented. The pattern of tobacco consumption was assessed through simple inquiries

including the smoking status, duration (in years), type of tobacco used (cigarette, cigar, hubble-bubble, others) and the frequency of smoking. The door-to-door survey, administration of the questionnaire and the collection of fasting blood samples was finalized in a 5 month period, during the winter when the average outside temperature ranged between 8-30ºC. Subjects who agreed to participate in the study were requested to be fasting overnight for a minimum of 12 hours before the blood was withdrawn. They were contacted 7–10 am in the morning and, under aseptic conditions, 2 venous blood samples were collected in 7-10 ml quantities. The first blood sample was collected in plane (without anticoagulant) tube for the estimation of triglycerides, total serum cholesterol (TSC), high-density lipoproteins (HDL), and blood sugar. The second blood sample was extracted in citrated tubes for the estimation of plasma fibrinogen. Collected blood samples were immediately transferred to the King Khalid University Hospital and College of Medicine Central Laboratory, Riyadh, for further processing and analysis. Duplicate measurements were carried out on all samples. Plasma fibrinogen was assayed by the clotting method as described by Ellis and Stransky.[24] Blood sugar, serum TC, HDL cholesterol and TG were assayed on Cobas Mira S Clinical Analyzer (Hoffman La Roche, Basel, Switzerland) using standard enzymatic colorimetric methods. Strict quality control was observed during the entire study. Assay performance was frequently monitored using the internal and external quality control sera for normal as well as abnormal (pathological) sera. Assay calibration was performed daily with strict compliance to the manufacturer's instructions. Based upon the participant's BMI, subjects were grouped into 4 categories according to the WHO classification: a BMI of 18.5-24.9 Kg/m^2 were considered as "Normal" while those with a BMI of 25.0-29.9 Kg/m^2 were classified as "overweight" and those whom BMI was 30.0-39.9 Kg/m^2 were considered "obese."[25-26] Morbid obesity was defined as BMI of ≥ 40 Kg/m^2. Plasma fibrinogen concentration of 140-400 mg/dl was considered as normal reference range for Saudi population.[27] Hypercholesterolemia was defined as mild when TSC was 5.2-6.2 mmol/l, and moderate to severe for the values >6.2 mmol/l. Hypertriglyceridemia was defined when the mean serum TG concentration was >2.3 mmol/l. Untreated hypertension was defined as mean clinical blood pressure of ≥90 mm Hg diastolic or ≥140 mmHg, or both systolic with no awareness of their hypertensive condition.[28] Hyperglycemia was defined when the fasting blood sugar exceeded 6.0 mmol/l. Only those patients who were not aware of being hypertensive or diabetic, or both until the time of blood collection were included in the final analysis. Known hypertensive or diabetics, or both receiving any respective medication(s) were excluded from the study.

Statistical methods. Subjects who were known hypertensive, hyperlipidemic, diabetic or on medication, or both for any type of CVD related etiology and who were not originally identified, were excluded during the final statistical analysis. Data were processed and analyzed using the Statpack Gold® statistical analysis package. Results are reported as mean ± standard deviation unless otherwise stated. Student's t- test (two-tailed) was used to examine the significance of difference in mean plasma fibrinogen concentrations between 2 sets of data, and p value <0.05 was considered significant. The Spearman Correlation Coefficients were calculated to examine the correlation between plasma fibrinogen and the lipids, BP, BMI, fasting blood sugar and tobacco consumption. The one-way analysis of variance (ANOVA) was used to test the significance of means between more than 2 groups.

Results. After excluding the samples with inadequate serum quantity or incomplete information, results of 2263/2358 subjects, consisting of 1934 (85.5%) men and 329 (14.5%) women are presented. The majority of the subjects (64%) were in the age groups of 21-40-years, men (65%) and women (56.5%). The mean ± SD plasma fibrinogen concentration in the entire sample of 2263 Saudi adults was 336 ± 115 mg/dl. Our results showed that the mean plasma fibrinogen increased gradually with age among Saudi adults, from 301 ± 108 mg/dl (age group 20-years) to 443 ± 132 mg/dl (age group 61-70-years). This increase in the fibrinogen level was statistically significant as we go down from the age group 20–30-years (p value 0.015) to the older age group 61-70-years (p=0.000). However, subjects aged >70-years did not show a significant difference in the mean plasma fibrinogen than subjects in the age group 61-70-years (p=0.912). Gender stratification showed that women overall had significantly higher plasma fibrinogen than men (p=0.0003). The gradual and consistent rise in the mean plasma fibrinogen with age, as observed in the total adult sample, was also seen among males. However, it could be noted among women after the age of 40 years without any statistical significance (p=0.091 to p=0.209). The mean plasma fibrinogen in female subjects was significantly higher than male subjects of the comparable age groups until the age group 31-40-years (p=0.068, p=0.005 and p=0.008,) after which the trend shifted towards males of age group 61-70-years. **Table 1** outlines the distribution of the studied subjects according to the defined fibrinogen reference intervals and gender. Of the 2263 subjects 1653 (73%) had their mean plasma concentration within the defined normal reference range of

141-400 mg/dl, whereas 556 (24.6%) were above and 54 (2.4%) were below the normal reference range. Majority of the men (73.8%) and women (68.7%) had their plasma fibrinogen within the normal reference range, however, hyperfibrinogenemia (plasma fibrinogen >400 mg/dl) was more frequent (31%) in women than men (23.5%). The quantitative relation between defined reference ranges of plasma fibrinogen and known CVD risk factors among the studied Saudi adults showed significantly higher systolic BP than those with normal (141-400 mg/dl) plasma fibrinogen (p=0.0001 and 0.0009). Moreover, women with elevated plasma fibrinogen (>400 mg/dl) had slightly raised systolic BP then hyperfibrinogenemic men (p=0.214). Significantly higher diastolic BP was noted among male subjects with elevated plasma fibrinogen (>400 mg/dl) than those with normal fibrinogen levels (p=0.000). On the other hand, women with plasma fibrinogen levels >400 mg/dl, as compared to those with normal fibrinogen levels, did not show a significant increase in their diastolic BP (p=0.211). Mild hypercholesterolemia was seen in both men and women with fibrinogen levels >400 mg/dl (p=0.000 and 0.06). There was a gradual and significant increase in mean TG concentration from 1.95 ± 1.4 mmol/l to 2.3 ± 1.2 mmol/l (p=0.000) among men as the plasma fibrinogen level increased from 400 mg/dl to >400 mg/dl. However, among women, the TG level decreased from 2.02 ± 1.6 mmol/l to 1.87 ± 1.65 mmol/l (p=0.437) as the plasma fibrinogen level increased from 400 mg/dl to >400 mg/dl. A reciprocal relation was observed between HDL and plasma fibrinogen level in both men and women. This relation was more significant in women (p=0.000) than men (p=0.484). There was a positive and significant association between BMI and plasma fibrinogen both in men (p=0.000) and women (p=0.000). All the subjects with fibrinogen level >400mg/dl were overweight and approaching the obesity scale (30.0-39.9 kg/m^2). Elevated plasma fibrinogen (>400 mg/dl) was also found to be associated with higher level of fasting blood sugar (FBS) among male subjects as compared to those with normal fibrinogen levels (p=0.0002). However, the relation between high FBS and hyperfibrinogenemia was not significant (p=value 0.200) among female subjects. **Table 2** shows the distribution of studied Saudi adults according to the smoking status and mean plasma fibrinogen. Of the 2263 participants, 492 (21.7%) declared themselves as "smokers" while 1771 (78.3%) did not give any history of smoking for the last 6 months and, therefore, were categorized as "non-smokers". Majority (81.9%) of the smokers were male while 18.1% were female. There was no significant difference in the overall distribution of mean plasma fibrinogen between smokers and non-smokers (p=0.624).When analyzed according to gender, it was noticed that mean ± SD plasma fibrinogen in male smokers (334.20 ± 122.30 mg/dl) was slightly higher than male non-smokers (332.0 ± 111.16 mg/dl), p=0.730. On the contrary, female smokers had slightly lower plasma fibrinogen (348.0 ± 93.12 mg/dl) than female non-smokers (361.0 ± 124.32 mg/dl), p=0.370. The mean plasma fibrinogen in female smokers was also higher than male smokers (p=0.317) and non-smokers (p=0.183). The distribution of studied subjects by smoking status was further stratified according to the defined fibrinogen reference intervals. Majority of the smokers (74.%) had their mean plasma fibrinogen (291.8 ± 65.0 mg/dl) within the normal reference range of 141-400 mg/dl. This was slightly higher than non-smokers (285.9 ± 60.80 mg/dl; p=0.109) under the same reference range. One hundred and twenty (24.4%)

Table 1 - Distribution of studied Saudi adults according to the defined plasma fibrinogen reference range and gender.

Fibrinogen reference range*	Male n (%)		Female n (%)		Total n (%)	
≤140 mg/dl	53	(2.7)	1	(0.3)	**54**	**(2.4)**
141-400 mg/dl	1427	(73.8)	226	(68.7)	**1653**	**(73)**
>400 mg/dl	454	(23.5)	102	(31)	**556**	**(24.6)**
Total	**1934**	**(85.5)**	**329**	**(14.5)**	**2263**	**(100)**

*King Khalid University Hospital reference range

Table 2 - Distribution of studied Saudi adults according to the smoking status and mean plasma fibrinogen.

Total subjects	Smokers n (%)	Non-smokers n (%)	*p* value
N=2263	492 (21.74) Male Female 403 (81.9) 89 (18.1)	1771 (78.26)	
Fibrinogen (mg/dl)	342.2 ± 106.34	345 ± 116.3	0.624
Male (n=1934)	403 (20.84)	1531 (79.16)	
Fibrinogen (mg/dl)	334.20 ± 122.30	332.0 ± 111.16	0.730
Female (n=329)	89 (27)	240 (73)	
Fibrinogen (mg/dl)	348.0 ± 93.12	361 ± 124.32	0.370
p value	0.317	0.0002	

smokers had their plasma fibrinogen >400 mg/dl with a mean of 489.00 ± 101.6 mg/dl. The non-smokers group had slightly less plasma fibrinogen (480.4 ± 84.0 mg/dl) as compared to smokers (p=0.343). Majority of the smokers were cigarettes smokers (84%), while 15% reported the use of hubble-bubble, one person (0.2%) reported cigar smoking, and 4 (0.8%) gave a history of undefined smoking habits. There was no significant difference (p=0.903) in the distribution of plasma fibrinogen between cigarette smokers (338.10 ± 120.61 mg/dl) and hubble-bubble users (336.30 ± 98.93 mg/dl). Approximately 39.7% of the cigarette smokers reported smoking 11-20 cigarettes per day, followed by 1-10 cigarettes per day (30.5%). Sixty-four (15.5%) of the smokers were smoking >30 cigarettes/day while 14.3% were smoking 21-30 cigarettes/day. All the smokers, regardless of the number of cigarettes smoked per day, had their mean plasma fibrinogen <400 mg/dl. A definite relation between the frequency of smoking (number of cigarettes/day) and the mean plasma fibrinogen could not be seen in our studied smokers. However, a reciprocal relation was observed between mean plasma fibrinogen and duration of smoking. For example, 83 (16.9%) of the smokers who gave a history of 1-5 years of smoking had significantly higher plasma fibrinogen (350.60 ± 132.0 mg/dl) than 95 (19.3%) smokers who smoked for 16-20 years (313.16 ± 95.79 mg/dl; p=0.032). **Table 3** highlights the prevalence and magnitude of various CVD risk factors among 492 smokers and 1771 non-smokers. Of all the studied risk factors, only triglycerides were found to be significantly higher in smokers (2.21± 0.005mmol/L) than non-smokers (2.04 ± 0.4 mmol/L; p=0.020). Other risk factors, such as cholesterol, and systolic/diastolic BP were slightly raised among smokers than non-smokers (p=0.450, p=0.141a and p=0.202,). HDL cholesterol, FBS and BMI showed minor trend towards higher values among non-smokers than smokers (p=0.220, p=0.308, and p=0.188). According to our results, the increase in the mean serum levels of TC, systolic/diastolic BP and BMI was significantly associated with a corresponding rise in the mean plasma fibrinogen levels among men and women. Hypertriglyceridemia and plasma fibrinogen were positively related in men while a slight inverse relation was seen in women. The mean plasma fibrinogen level showed a slight insignificant decrease with increasing HDL cholesterol in men, however, it was significantly higher (p=0.01) among women who had their HDL cholesterol >1.6 mmol/l. BMI showed an equally strong positive association with plasma fibrinogen both in men and women. Both men and women with elevated fasting blood sugar (>6.0 mmol/l) had significantly higher plasma fibrinogen than those with normal sugar levels (p=0.000). It was also noted that hyperglycemic women had significantly higher fibrinogen than hyperglycemic men (p=0.0083). **Table 4** shows Spearman's correlation coefficient (rs) between mean plasma fibrinogen (mg/dl) and modifiable CVD risk factors among adult Saudi men and women. Our results showed a strong correlation of equal magnitude in both genders (rs 0.30 and 0.14) between mean plasma fibrinogen, BMI and total cholesterol. Systolic blood pressure was slightly higher in women than in men (rs 0.26 and 0.22,). Diastolic blood pressure was more correlated to plasma fibrinogen in men (rs=0.20, p=0.000) than in women (rs 0.13, p value of 0.016). A weak but statistically significant correlation (rs 0.10, p=0.013) was noticed between serum triglycerides and plasma fibrinogen in men whereas an insignificant, negative correlation

Table 3 - Distribution of cardio-vascular disease risk factors (mean ± SD) among Saudi smokers and non-smokers.

CVD risk factors	Smokers (n=492)	Non-smokers (n=1771)	*p* value
Fibrinogen (mg/dl)	342.12 ± 106.34	345.20 ± 116.30	0.624
Cholesterol (mmol/L)	5.20 ± 1.15	5.175 ± 20.45	0.450
HDL cholesterol (mmol/L)	1.08 ± 0.02	1.125 ± 0.0.8	0.220
Triglycerides (mmol/L)	2.21 ± 0.05	2.04 ± 0.4	0.020
FBS (mmol/L)	5.54 ± 0.913	5.56 ± 0.946	0.308
BP, systolic (mm Hg)	122.37 ± 11.62	121.36 ± 18.84	0.141
BP, diastolic (mm Hg)	80.00 ± 11.68	79.50 ± 11.82	0.202
BMI (kg/m^2)	27.14 ± 5.15	27.4 ± 5.23	0.188
Age (years)	38.00 ± 13	37.6 ± 12.5	0.307

CVD - cardiovascular diseases, HDL - high density lipoprotein, FBS - fasting blood sugar, BP - blood pressure, BMI - body mass index

Table 4 - Spearman's correlation coefficient (rs) between mean plasma fibrinogen (mg/dl) and cardiovascular diseases risk factors among adult Saudi subjects.

Risk factors	Male		Female	
	rs	*p* value	*rs*	*p* value
Body mass index	0.30	0.000	0.30	0.000
Blood pressure				
Systolic	0.22	0.000	0.26	0.000
Diastolic	0.20	0.000	0.13	0.016
Total cholesterol	0.14	0.000	0.14	0.009
Triglycerides	0.10	0.013	-0.02	0.506
High density lipoprotein	-0.03	0.144	0.02	0.713
Fasting blood sugar	0.101	0.0001	0.187	0.0012

(rs-0.02, p=0.506) was present in women. High density lipoprotein cholesterol showed an insignificant negative correlation with mean plasma fibrinogen in men and a slight insignificantly positive correlation in women. Fasting blood sugar appeared to be better correlated to plasma fibrinogen in women (rs=0.187, p=0.0012) than men (rs=0.1010, p=0.0001).

Discussion. Fibrinogen is an acute phase reactant, soluble plasma protein with a molecular weight of 340 kg Dalton, normally present at a concentration of 250-350 mg/dl, and with a half-life of 3-5-days. In addition to its key role in the clot (thrombus) formation, fibrinogen promotes platelet aggregation, increases blood viscosity, stimulates smooth muscle cell migration and proliferation, and may show mitogenic and angiogenic properties.[12,29] Moreover, after binding to the lipoprotein in the vascular intima, fibrinogen may enhance the accumulation of extracellular lipids in fibrous plaques.[29-30] Plasma levels of fibrinogen may rise in response to trauma, tissue inflammation (atherosclerotic process), pregnancy as well as the introduction of biological stimulators such as growth hormones, thrombin, prostaglandins, and endotoxins.[31] Meade et al[11] were the first to identify plasma fibrinogen as an independent risk factor for ischemic heart disease in the middle-aged white men during 4-years and 10-years follow up periods.[12] Since then, several studies have established the association between plasma fibrinogen and CVD.[12-21] Raised fibrinogen levels have repeatedly been shown to predict cardiovascular events with a power as strong as that of TC levels.[12,13,21] An increase in the mean plasma fibrinogen concentration by one standard deviation was accompanied by a 70% increase in death rate from ischemic heart disease.[12] Higher plasma fibrinogen level has been associated with angiographic severity of the disease, recurrent ischemic events, post-angioplasty re-stenosis risk and myocardial infarction.[12,31-35] In the present cross-sectional study, the mean plasma fibrinogen levels of healthy adult Saudi men and women, living in a heterogeneously populated urban area in Riyadh, were studied in relation with modifiable CVD risk factors. The overall mean plasma fibrinogen of our subjects was found to be within the normal reference ranges for Saudi population.[27] Ethnic origin has been reported to affect the normal fibrinogen levels dark skin color has been associated with higher and white skin color has been related to lower plasma fibrinogen levels.[19] However, the mean plasma fibrinogen levels of our subjects, despite being of different racial origin, were surprisingly in close agreement with 2 Caucasian populations (Henreich et al,[23] 330 mg/dl; and Eliasson et al, 330-350 mg/dl).[23,36] Our results were also in partial agreement with those reported by Jourban et al.[37](Syrian study; 313 ± 89 mg/dl). In addition to genetic or racial characteristics, social and cultural factors have also been shown to affect the normal fibrinogen levels. In a recent study, Yano et al[38] compared fibrinogen levels between adult Japanese living in Japan with those living in Hawaii (USA) and found out that, despite common ethnic origin, mean plasma fibrinogen level of Japanese-American men (307 mg/dl) was significantly higher than native Japanese (270 mg/dl). In our opinion, the effect of racial (genetic) as well as the socio-cultural factors on the normal plasma fibrinogen level is not yet fully elucidated and needs further investigations. Age-adjusted results showed that an increase in the age was accompanied by a corresponding rise in the mean plasma fibrinogen thus indicating a positive correlation between age and plasma fibrinogen. This increase was more significant in the age groups 41-50, 51-60 and 61-70-years (p value 0.000). These findings are in accordance with previous reports from KSA[27] and Western countries.[13,39-45] However, the increase in the mean plasma fibrinogen level was not significant in the age group 21-30-years and those above 70-years of age. Increase in the fibrinogen level with age has been associated with an increase in the incidence of coronary heart disease in men and women under 70-years of age.[13] When tabulated according to sex, the overall mean plasma fibrinogen was significantly higher (p=0.0003) in women than men. Gender-associated differences in the plasma fibrinogen concentration are well documented and has been attributed to the method of fibrinogen estimation.[20,27,40,44,46-47] For example, in Barasch et al's,[46] BIP study, sex-related difference in the mean plasma fibrinogen level was detected only when fibrinogen was determined directly by the Hemker's method. Similarly, Scottish Heart Health study reported a difference between men and woman for a middle-aged population when fibrinogen was determined by the clotting method but not when measured by the heat precipitation method.[44] The presence of higher plasma fibrinogen in our female subjects may likely be due to the fact that we also used the clotting method of Ellis and Stransky.[24] In addition to the genetic/social factors, the presence of significant differences in the plasma fibrinogen levels reported by various studies may partly be due to the lack of a unified or standardized method for the estimation of plasma fibrinogen. Hyperfibrinogenemia is a well documented risk factor for coronary heart diseases and related cardiovascular mortalities.[12,32-35] Higher plasma fibrinogen levels have been associated with stroke, myocardial infarction and ischemic heart disease.[12,13,15,18,21] Though majority of our men

(73.8%) and women (68.7%) had their plasma fibrinogen within normal reference range of 141-400 mg/dl, however, considerable number of men (23.5%) and women (31%) did show elevated (>400 mg/dl) fibrinogen levels (**Table 1**). Moreover, it was also noted that hyperfibrinogenemia was significantly more prevalent among our studied Saudi women than men (p=0.0049). The presence of significantly elevated blood pressure (both systolic and diastolic), serum total cholesterol, triglycerides, and BMI in hyperfibrinogenemic (>400 mg/dl) men; and high blood pressure (systolic), cholesterol and BMI among hyperfibrinogenemic women clearly supports the earlier reports indicating that raised fibrinogen concentration may play an active role in precipitating most of the CVD risk factors.[19-20] The existence of a weak, reciprocal association between HDL cholesterol, triglycerides and elevated plasma fibrinogen level (>400 mg/dl) among women, and a weak, positive relation between HDL and hyperfibrinogenemia in men is in partial agreement with previous reports.[43,45-46] Kannel et al[48] (Framingham Study) reported that, in addition to other CVD risk factors, diabetics also had significantly higher levels of plasma fibrinogen, and the rise in fibrinogen was observed throughout the range of blood sugar levels. Recent studies have also indicated that increased plasma fibrinogen is associated with prevalence of diabetes mellitus and other familial and metabolic risk factors.[13,39-45,49-50] Presence of significantly higher levels of FBS (though still within the normal reference range) in our hyperfibrinogenemic men is in agreement with Imperatore et al who also reported elevated FPS (5.58 ± 0.044 mmol/l) among their hyperfibrinogenemic males (≥350 mg/dl) as compared to those with normal plasma fibrinogen levels (<350mg/dl; FBS 5.51±0.017 mmol/l).[51] The presence of significantly higher mean plasma fibrinogen among our hyperglycemic subjects (who were not aware of their diabetes prior to this survey) is in agreement with and Margaglione et al[49] and Ko et al[50] who have also reported a significant association between increased plasma fibrinogen and diabetes mellitus. Chronic tobacco smoking has been associated with a significant increase in the risks of coronary diseases, occlusive arteriopathy of the lower limbs and cerebral vascular accident.[51-54] The risk is strongly augmented by the presence of other vascular risk factors such as hypertension, hypercholesterolemia, obesity and diabetes. Nicotine and carbon monoxide are reported to play a major role in the effect of smoking on vessels.[52-54] In addition to its acute hemodynamic effects, tobacco not only has an atherogenic effect (endothelial toxicity and changes in lipid profile) but it also facilitates thrombosis by alteration of platelet functions and elevation of plasma fibrinogen level, hematocrit level and blood viscosity.[52-54] Several studies have reported a positive correlation between tobacco smoking and plasma fibrinogen among both men and women.[55-57] However, our results did not show any significant difference in the distribution of mean plasma fibrinogen between smokers and non-smokers except that female smokers had slightly raised fibrinogen than male smokers (p=0.317, **Table 1**). Moreover, the increase in the number of cigarettes smoked per day or the duration (years) of smoking in our studied subjects was not accompanied by a corresponding increase in the plasma fibrinogen as reported by others.[55-57] Instead, a slight reciprocal relation was seen between years of smoking and the plasma fibrinogen. The absence of a positive correlation between smoking and plasma fibrinogen among our studied smokers might be due to the environmental and genetic factors[58-59] and therefore, needs further investigations. Authors would also like to emphasize here that due to certain religious beliefs, smoking is not appreciated by Saudi society. Therefore, the reliability of participant's response who denied smoking needs to be considered as well! Nevertheless, our results appear to be in partial agreement with Rosengren and Wilhelmsen[60] who also reported higher fibrinogen concentration in some of their non-smokers. The difference in the magnitude of metabolic as well as modifiable CVD risk factors between smokers and non-smokers was not significant, except for serum triglycerides which were significantly higher in smokers than non-smokers (p=0.020, **Table 3**). This is in partial agreement with Hughes et al who also reported higher mean serum triglycerides and lower HDL-cholesterol in smokers.[57] The presence of a significant correlation between serum total cholesterol and plasma fibrinogen among our studied men and women is consistent with most of the previous reports from other countries.[15,21,36,39,44,46,61-66] However, our data have shown a slightly higher association in women than in men, as reported by others.[36] A total of 14.3% of our adult population were found to be hypercholesterolemic (cholesterol >6.2 mmol/l) in whom plasma fibrinogen level was significantly raised (p=0.003) than subjects with normal serum cholesterol concentration. Experimental studies in animal models have shown that plasma fibrinogen levels were elevated when animals were maintained on cholesterol-rich diet.[67-68] This implies that lowering the in-take of cholesterol may result in a corresponding decrease in the plasma fibrinogen level. The correlation between plasma fibrinogen and HDL-cholesterol did not appear to be significant in our study. It was inconsistent in men and slightly elevated in women (p=0.713). Previous reports have also documented either a negative correlation[39,65-66,69] or a weak positive correlation between plasma fibrinogen and HDL

cholesterol.[16,37,39-45] Although, the mean plasma fibrinogen in women with HDL cholesterol >1.6 mmol/l was significantly higher than those with lower HDL level (p=0.01), yet the overall correlation could not be conclusive due to the low number of female subjects in the study. The existence of an inverse or a negative correlation between HDL-cholesterol and plasma fibrinogen is not well understood. The presence of a weak but significant positive correlation between serum triglycerides and plasma fibrinogen in men and a negative insignificant correlation in women is in agreement with Barasch et al[46] but contradicting Balleisen et al[16] who reported a negative correlation in men and a positive correlation in women, and Eliasson et al[36] who also showed a strong positive correlation in women than men. In agreement with previous reports,[36-45,66] our study also showed a strong, highly significant (p=0.000) positive association between BMI and plasma fibrinogen both in men and women. According to our results, 483 (25%) of the males and 112 (34%) of the females were classified as obese (BMI ≥ 30 kg/m^2) and all of them had significantly elevated plasma fibrinogen levels as compared to subjects with BMI <30 kg/m^2. The age-dependent variations in the mean plasma fibrinogen are well documented.[13,39-40,42-43.45,66] In our study, the pattern of obesity, plasma fibrinogen and the age was almost consistent among both men and women. Numerous cross-sectional epidemiological studies have reported a modest positive correlation between plasma fibrinogen levels and blood pressure.[13,16,20,70-71] In our study, both men and women also showed a positive correlation between mean plasma fibrinogen and systolic/diastolic blood pressures thereby supporting earlier reports.[13,16,20,70-71] As per the definition, systolic hypertension (BP>140 mm Hg) and diastolic hypertension (BP >90 mmHg) was detected in 11.6% and 11% of our adult subjects. However, the correlation between systolic BP and mean plasma fibrinogen was slightly stronger in women than men. According to previous reports, elevated fibrinogen levels increases the blood viscosity thereby increasing the peripheral vascular resistance, which potentially elevate the blood pressure.[72] On the other hand, endothelial dysfunction accompanying high blood pressure have been said to increase the plasma fibrinogen or viscosity.[70] It is not yet clearly established whether elevated plasma fibrinogen is a cause or a consequence of high blood pressure.

In conclusion, the presence of hypercholesterolemia (14%), hypertriglyceridemia (24%), systolic (11.2%) and diastolic hypertension (10.2%), obesity (24.9%) and hyperglycemia (22.6%) among our studied hyperfibrinogenemic Saudi adults highlights the importance of plasma fibrinogen as a potential cardiovascular risk factor. Considering the encountered limitations due to the study design, no generalization of results is attempted. However, our findings intend to demonstrate the correlation between plasma fibrinogen and conventional CVD risk factors. The burden of CVD and its consequences are of sizable importance among Saudi population. This justifies the need to undertake large analytical, epidemiological studies representative of the Saudi population in order to establish the casual relationship and to determine the precise role of hyperfibrinogenemia as a potential CVD risk factor. Only then we would be able to broaden the application and interpretation of plasma fibrinogen levels in the actual clinical practice. Moreover, the effect of smoking on the plasma fibrinogen levels among Saudi population needs further investigations in relation to various confounding factors and determinants.

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