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ADVERSE EFFECT OF TOBACCO SMOKE ON RENAL DISEASE IN YOUNG HEALTHY MEDICAL STUDENTS: A CROSS SECTIONAL COMPARATIVE STUDY.

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ABSTRACT… Objectives: To compare the effect of active and secondhand smoke to unexposed smoke and to renal functions in young healthy Medical Students. **Study Design:** Cross sectional study comparative. **Setting:** Mohi-ud-din Islamic-Medical-College Mirpur AJ&K. **Period:** Fanuary-2018 to February-2019. **Material & Methods:** 350 healthy medical students aged 17-19 years were divided into active, secondhand and unexposed to smoke on basis of serum cotinine levels. The estimated GFR was measured by Modification of Diet in Renal Disease equation, albuminuria by albumin to urinary creatinine ratio, BMI by body weight (kg) to height (m2) and blood pressure by mercury manometer. The chronic kidney disease was classified into low, moderate and high risk according to Kidney Disease: Improving-Global Outcomes-2012-guidelines. **Results:** Out of 350 participants, 49 were active and 126 were of secondhand smoke. Most were male, overweight or obese, have high systolic and diastolic pressure and decreased eGFR. The CKD prevalence was 8.2%, eGFR <60ml/min/1.73 m^2 noticed in 19% and albuminuria in 26.4% of the participants. The proteinuria in active smokers in comparison with unexposed showed a high OR-5.67-(95%CI-17.17-40.49), cotinine levels >10 ng/mL; OR-5.520-(95%CI-3.67-3.91), systolic BP >140 mmHg; OR-2.50-(95%CI- 0.142-4.968); moderate to severely decreased eGFR, OR-2.478-(95%CI-0.124-4.391) and with high creatinine levels OR-4.300-(95%CI 2.432–7.603). The decreased eGFR showed Odds for obese OR-1.113(95%CI-2.391-5.197), active smokers OR-0.145(95%CI-0.029-0.721) and for systolic blood pressure >140 mmHg OR-6.892-(95%CI-1.414-2.235). **Conclusion:** Tobacco smoke exposure was associated with proteinuria and decreased eGFR effecting kidney functions in adolescents.

Key words: Chronic Kidney Disease, Estimated Glomerular Filtration Rate, Healthy Person, Proteinuria, Smoking.

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INTORDUCTION

Chronic kidney disease (CKD) is a global public health problem affecting all age groups.[1] The mean global prevalence of CKD, 13.4% for stages 1–5, is on increase and according to WHO, one of five adults with hypertension and one of three adults with diabetes have CKD. In 2010, 2.62 million patients were on dialysis worldwide and the figure will be doubled by 2030. In spite of spending >2–3% of the annual health-care budget, more than 969,000 annual deaths are resulted due to CKD globally.[2] Africans, Americans, and South Asians are at high risk of developing CKD[3]; while in Pakistani population, new end-stage renal disease is >100 cases per million per annum.[4]

Chronic kidney disease (CKD) is characterized by reduced kidney function with eGFR<60 mL/min/1.73 m^2 for 3 months or more irrespective of cause, ascertained by elevated serum creatinine levels and presence of albuminuria or albumin-creatinine ratio >30 mg/g in two of three spot urine specimens.[5]

The CKD is considered as one of the non-communicable disease among diabetes, cancer, cardiovascular disease, and chronic respiratory disease. Diabetes mellitus (14%) is the 2nd leading cause of CKD after chronic glomerulonephritis

(37%) while the hypertension represents as third major cause (9%).[6] The studies have shown the role of cigarette smoke in CKD along with its well-known decreased lung functions, delayed growth, increased risk of asthma, early atherosclerosis, neurocognitive defects, cancer, heavier smoking in adulthood and early childhood mortality.[7,8] The outcomes of CKD include renal failure, increased risk of cardiovascular disease (hypertension, heart failure, heart attack) and premature death.[9]

The pathogenesis of cigarette smoke induced CKD is not yet completely understood but may involve oxidative stress, arteriolar changes, loss of renal epithelial cells and podocytes, inflammation, inflammatory and cellular responses, deposition of extracellular matrix, apoptosis and or metabolic dysregulation.[5,10]

Studies are still lacking regarding association between CKD and active and secondhand smoke in generally healthy adolescents, because of vast heterogeneity in this age group, low incidence and less risk factors of CKD as hypertension and diabetes mellitus.[11]

The objective of this study is to see and compare the effect of active and secondhand smoke to unexposed smoke and renal functions in young healthy medical students.

METHOD

This cross sectional comparative study was conducted on 350 medical students of 1st and 2nd year MBBS at Mohi ud din Islamic Medical College Mirpur AJ&K and CMH Kharian Medical College aged 17 to 19 years from February 2018 to February 2019, after taking written consent from participants and approval from the institutional ethical committee. The participants with primary kidney disease, diabetes mellitus, severe hypertension, and with sign symptoms of CKD were excluded from the study. Five ml. blood sample was drawn under a-septic technique from the cubital vein to estimate serum cotinine and creatinine levels.

The serum cotinine (biomarker for tobacco exposure) levels were done on all students to assess tobacco smoke. The participants smoking actively or smoked only one cigarette or smoked one day last month or those with serum cotinine levels >10 ng/mL whether reported as nonsmoker were taken as active smokers. The participants who reported living with person who smoke, regardless their cotinine level, or had cotinine levels >0.05 ng/mL to <10 ng/mL even not living with smoker, were labelled as secondhand smoke; while the participants with cotinine levels <0.05 ng/mL, not living with a smoker and not smoked since the last month were taken as unexposed to tobacco.[12]

The height and weight was measured (after removing jacket and shoes) to calculate BMI by dividing body weight in kg to height in m2; and the participants were categorized as normal, overweight, and obese according to the WHO recommendation, BMI< 25 kg/m2; 25-30 kg/m^2; and BMI ≥ 30 kg/m2 respectively. Blood pressure was measured using mercury manometer in the sitting position after taking rest for 5 min or longer, and was graded into Normal BP = <120/<80 mm Hg; elevated BP = 120-129/<80 mm Hg; stage 1 hypertension = 130-139 or 80-89 mm Hg, stage 2 hypertension ≥140 or ≥90 mm Hg. The participants were labelled hypertensive after taking ≥2 readings on ≥2 occasions.[13]

To rate the CKD, we used the Kidney Disease: Improving Global Outcomes2012 (KDIGO 2012) criterion that takes presence of renal injury (albuminuria) and/or the decrease in eGFR.[14] We used albuminuria as a marker of renal injury, and was considered as the ratio between the concentration of urinary albumin and creatinine, equal to or greater than 30 milligrams of albumin per gram of creatinine. The eGFR was estimated by the Cockcroft-Gault Modification of Diet in Renal Disease (MDRD) study equation.[15] The calculated values below 60 ml/min/1.73m2 was taken as reduced.[16]

MDRD equation =186 x (Creatinine/88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black). The serum creatinine was measured by coupled enzymatic assay and the corrected creatinine level was calculated by Corrected creatinine = -

0:016 (0:9783 x Creatinine).[17]

The first urine sample was collected for measuring urinary creatinine and albumin levels to calculate proteinuria.

DATA ANALYSIS

Data were entered into a Microsoft Excel 2003 spreadsheet and analyzed, using the SPSS 18.0.1. The demographics and outcome variables were summarized using descriptive summary measures, expressed as percentage for categorical variables. Chi-Square test was used to compare the variables while Student 't' test was used for quantitative variables. Multivariate logistic regression used to identify the independent predictor variables. Adjusted matched odds ratio with its corresponding 95% confidence interval was used and significance was taken at *P*-value less than 0.05.

RESULTS

Table-I shows demographic, clinical and laboratory characteristics of adult participants according to smoking status. There are 350 participants, out of which 49 were active smoker, 126 secondhand smoker while 175 were not exposed to smoke. A statistically significant difference ($p<0.05$) was noticed regarding BMI, creatinine, and eGFR when active smokers were compared to secondhand smoker, however, age, pulse, systolic and diastolic blood pressure were found to be non-significant ($p>0.05$). The difference between active smoker and unexposed participants was also found statistically significant ($p<0.05$) when age, pulse, BMI, creatinine, eGFR and systolic blood pressure were compared, while diastolic pressure was found to be non-significant. A same trend of significant difference ($p<0.05$) was noticed for age, pulse, creatinine, and eGFR between the secondhand smoke and those who were not exposed to smoke, however, BMI systolic and diastolic blood pressure were found non-significant.

Table-II shows comparison between male and female participants. A significant difference ($p<0.05$) between the male and female participants was noticed when age, pulse, BMI, and creatinine were compared, however, the comparison was found to be non-significant ($p>0.05$) when eGFR, systolic and diastolic pressure were compared.

Table-III showed tobacco smoke exposure status by participant characteristics. Most of active smokers (n-46) were male (93.9%), overweight (n- 18, 36.7%) or obese (n-11, 22.4%), with high creatinine levels (n-36, 73.5%), mild to moderate (n-10, 20.4%) to severe decreased eGFR (n-02, 4.1%), high systolic pressure >140 mmHg (n-05, 10%) and (n-04, >8%) have diastolic pressure >90 mmHg. All active smokers with their cotinine levels >10 ng/mL showed proteins in their urine (n-11, 22.4%). The secondhand smokers (n-126) were also mostly male (n-102, 81%), overweight (n-31, >24%), obese (n-07, 5.6%), showed high creatinine level (n- 28, 22.2%), mild to moderate decreased eGFR (n- 07, 5.6%), systolic pressure >140 mmHg (n- 03, 2.4%) and diastolic pressure >90 mmHg (n-03, 2.4%), however, urine positive for proteins was noticed in (n-05, 4%) of cases. Most of unexposed were female (n-148, 84.6%) have normal BMI (n-108, 61.7%), normal creatinine levels (n-173, >98%) and eGFR (n-164, 93.7%). Most of the unexposed participants (n-105, 60%) were in normal range of systolic and diastolic blood pressure and did not show any proteins in urine.

Table-IV shows Multiple Logistic Regression with respect to proteinuria and low eGFR. The proteinuria in active smokers and secondhand smokers showed a significantly high OR, 5.67 (95 % CI, 17.170 - 40.49) and OR, 3.25 (95 % CI 3.67–3.98) respectively compared to unexposed. A same trend was seen with cotinine levels >10; OR, 5.520 (95 % CI, 3.679 – 3.917) compared to non-exposed. A significant difference was noticed for systolic BP >140 mmHg; OR, 2.50 (95 % CI 0.142 – 4.391); severely decreased GFR OR, 2.478 (95 % CI 0.124 – 4.319) and for high creatinine levels OR 4.300 (95 % CI 2.432 –7.603) compared to non-exposed. The obese had no significant effects on development of proteinuria and showed a low odds ratio 0.653 (95% CI – 0.073 - .812).

The Multiple logistic Regression analyses with moderate to severely decreased eGFR in the study groups showed a significant ($p<0.05$) high OR of 6.892 (95 % CI 1.414–2.235) with systolic blood pressure >140 mmHg; obese OR of 1.113 (95% CI, 2.391 – 5.197) and overweight OR 2.433 (95% CI, 2.497 - 2.908) participants. A same trend was also seen with active smokers OR, 0.145 (95% CI, 0.029 – 0.721). Low GFR showed non-significant ($p<0.05$) low OR of 0.498 (95% CI, 0.058 – 4.304) with diastolic pressure >90mmHg, while an OR, 2.001 (95% CI, 0.816 – 4.905) with high creatinine, and an OR, 1.382 (95% CI, 0.323-5.913) with proteinuria in active smokers compared to unexposed.

Figure-1 shows the CKD prognosis considering categories of GFR and albuminuria. Out of 350 participants 321 (green - 91.7%) were at low risk; 22 (purple – 6.3%) at moderately increased risk; 06 (blue – 1.7%) had high risk and 01 (red – 0.3%) were at very high risk of developing end-stage chronic kidney disease.

Green	low risk
Purple	moderate risk
Yellow	high risk
Red	very high risk.

Variable	Active Smoker Group 1 (n-49)	2nd hand smoker Group 2 (n-126)	Unexposed Group 3 (n-175)	P-Value 1 &2	P-Value 1 &3	P-Value 2 &3
Age	20.24±1.47	19.99±1.21	19.84±1.03	0.246	0.030	0.042
Pulse	69.80±7.15	71.25±10.59	76.70±11.46	0.379	0.000	0.000
BMI	25.45±4.87	23.00±3.89	22.49±3.78	0.001	0.000	0.255
Creatinine	105.69±47.72	74.86±26.86	67.11±20.50	0.000	0.000	0.005
eGFR	75.57±20.67	82.20±18.01	89.77±16.04	0.037	0.000	0.000
Systolic BP	117.14±13.65	113.65±10.20	112.66±11.23	0.067	0.020	0.435
Diastolic BP	76.12±9.53	74.76±8.64	75.38±7.17	0.365	0.558	0.494

Table-I. Comparison of demographic, clinical and laboratory characteristics of adult participants according to smoking status.

Variable	Male (N-175)	Female (N-175)	P-Value
Age	20.22±1.34	19.69±0.915	0.000
Pulse	69.52±8.73	78.02±11.45	0.000
BMI	24.09±4.37	22.08±3.54	0.000
Creatinine	83.66±37.13	66.94±19.04	0.000
eGFR	84.49±18.28	85.62±18.08	0.563
Systolic BP	114.60±10.86	112.69±11.71	0.115
Diastolic BP	75.07±8.90	75.15±7.15	0.658

Table-II. Comparison between male and female participants regarding study variables.

Variable	Active smoker (n-49)	Secondhand smoker (n-126)	Unexposed (n-175)	P-Value
Sex Female (n-175) Male (n-175)	03 (6.1%) 46 (93.9%)	24 (19.0%) 102 (81.0%)	148 (84.6%) 27 (15.4%)	0.000
BMI Normal <25 Overweight 25-30 Obese >30	20 (40.8%) 18 (36.7%) 11 (22.4%)	88 (69.8%) 31 (24.6%) 07 (5.6%)	108 (61.7%) 54 (30.9%) 13 (7.4%)	0.001
Creatinine (ng/mL), Normal High	13 (26.5%) 36 (73.5%)	98 (77.8%) 28 (22.2%)	173 (98.9%) 02 (1.1%)	0.000
eGFR (mL/min per 1.73 m2), Normal (>90) Slightly decreased (60-89) Mild to moderate decreased (45-59) Moderate to severe (30-45)	14 (28.6%) 23 (46.9%) 10 (20.4%) 02 (4.1%)	55 (43.7%) 64 (50.8%) 07 (5.6%) 00 (0%)	164 (93.7%) 11 (6.3%) 00 (0%) 00 (0%)	0.000
Systolic Blood pressure (mmHg) <120 120-129 130-139 >140	31 (63.3%) 09 (18.4%) 04 (8.2%) 05 (10.2%)	79 (62.7%) 34 (27.0%) 10 (7.9%) 03 (2.4%)	105 (60.0%) 55 (31.4%) 12 (6.9%) 03 (1.7%)	0.066
Diastolic Blood pressure (mmHg) <80 80-85 86-90 >90	20 (40.8%) 18 (36.7%) 07 (14.3%) 04 (08.2%)	50 (39.7%) 51 (40.5%) 22 (17.5%) 03 (2.4%)	64 (36.6%) 82 (46.9%) 28 (16.0%) 01 (0.6%)	0.076
Cotinine level (ng/mL) <0.05 0.05-10 >10	0 (0%) 0 (0%) 49 (100%)	0 (0%) 126 (100%) 0 (0%)	175 (100%) 0 (0%) 0 (0%)	0.000
Urine protein <3 mg- nmol 3-30 mg-nmol	38 (77.6%) 11 (22.4%)	121 (96%) 05 (4%)	175 (100%) 00 (0%)	0.000

Table-III. Tobacco smoke exposure status by participant characteristics in Adolescents.

DISCUSSION

Considering the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for diagnosing and managing chronic kidney disease, our results showed 321 (91.7%) participants at low risk of developing chronic kidney disease while 22 (6.3%) participants at moderate risk for stage 1 and 2 chronic kidney disease mostly in patients with moderate albuminuria and mild to moderately decreased eGFR, 06 participants (1.7%) showed high risk while only one (0.3%) showed very high risk of developing CKD, however, none was found in stage 4 or 5 of renal failure. The main risk factors associated with CKD in our study were: male gender, active smoker with high cotinine levels, raised BMI and high systolic blood pressure. Globally, the prevalence of all CKD stages ranges between 8-16%, as seen in our study.[14] Certain studies showed a low CKD prevalence as these studies either consider the current CKD classification or included eGFR and/or albuminuria in diagnosis of CKD.[18,19]

Our results are consistent with a number of studies which showed raised arterial pressure with or without diabetes as an important and main risk factor of end-stage renal disease.[20, 21]

Variables	Standard Error	Odds ratio	95% Confidence Interval	P-Value
Smoker Unexposed Secondhand Active	 0.653 0.610	 3.251 5.679	 3.67–3.987 17.17 - 40.49	 0.000 0.000
Cotinine (ng/ml) <0.05 0.05-10 >10	 0.456 0.571	 3.679 5.520	 1.607 – 1.717 3.679 – 3.917	 0.000 0.000
BMI 25-30 >30	 1.067 1.115	 0.687 0.653	 0.085 - 5.557 0.073 – 5.812	 0.725 0.703
Creatinine (high)	0.291	4.300	2.432 – 7.603	0.000
eGFR slightly decreased Moderate Severe	 1.501 1.476 1.511	 5.250 1.333 2.478	 3.018 – 10.966 0.850 – 2.510 0.124 – 4.391	 0.007 0.064 0.562
Systolic blood pressure ≤120 120-129 130-139 >140	 0.646 0.677 0.781	 1.855 3.167 2.500	 0.217 – 15.814 0.300 – 3.374 0.142 – 4.968	 0.014 0.012 0.049
Diastolic BP ≤80 81-90 >90	 0.840 0.841 0.879	 8.824 11.613 11.250	 1.700 – 45.803 2.234 – 60.366 2.010 – 62.973	 0.010 0.004 0.006
Multiple logistic regression analyses on association of variables with proteinuria in the study groups.				
Variables	**Standard error**	**Odds ratio**	**95% Confidence Interval**	**P-Value**
Proteinuria	0.503	1.382	0.323 – 5.913	0.008
Creatinine (high)	0.457	2.001	0.816 – 4.905	0.129
BMI <25 25-30 >30	 1.162 0.785	 2.433 1.113	 2.497 - 2.908 2.391 – 5.197	 0.000 0.000
Systolic blood pressure ≤120 120-129 130-139 >140	 1.339 1.542 0.109	 7.307 6.123 6.892	 2.831 – 6.054 1.682 – 3.982 1.414 – 2.235	 0.000 0.000 0.000
Diastolic BP ≤80 81-90 >90	 1.054 1.039 1.100	 0.734 0.528 0.498	 0.093 – 5.792 0.069 – 4.047 0.058 – 4.304	 0.769 0.539 0.527
Smoker Unexposed Secondhand Active	 0.683 0.819	 0.509 0.145	 0.134 – 1.938 0.029 – 0.721	 0.322 0.018

Table-IV. Multiple logistic regression analyses on association of variables with proteinuria in the study groups.

GFR Category		Albumin category		
		<3 mg/mmol Normal to mild	3-30 Moderate raised	>30 Severely raised
		A1	A2	A3
>90 Normal	G1	229 (65.4%)	04 (1.1%)	-
Mild 89-60	G2	92 (26.3%)	06 (1.7%)	-
59-45 Mild to moderate	G3a	12 (3.4%)	05 (1.4%)	-
44-30 Moderate to severe	G3b	01 (0.28%)	01 (0.28%)	-
29-15 Severe reduction	G4	-	-	-
<15 Kidney failure	G5	-	-	-

Table-V. Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria category.

In the United States, approximately 26% of the people with hypertension have CKD; a study done in Mississippi[22] showed that patients with more than one risk factors like hypertension, and diabetes have about twice the prevalence of low GFR and albuminuria compared to those with one factor, and declared that timely management of diabetes and hypertension decreases the rate of mortality due to CKD. The hypertensive renal disease depends on the degree of failure of the auto regulatory mechanisms that prevent BP elevation transmitted to the renal microvasculature and starting a vicious cycle of hypertension with a gradual decrease in GFR.[10,20-22]

In our results 19 (30.1%) participants having eGFR less than 60 ml/min/1.73 m2, and Multi logistic Regression analysis showed a significant association with albuminuria, raised BMI, and systolic pressure >140 mmHg. The National Health and Nutrition Examination Survey surveys of 1988-1994 and 1999-2004 (NHANES), after full adjustment of variables, found a prevalence of albuminuria and low GFR more strongly linked to hypertension.[23] Both diabetes and high blood pressure can cause damage to the kidneys, decreased GFR and proteinuria. Our study participants with active smoking showed (n-12, 24.5%) decreased eGFR <60 ml/min/1.73 m2 and high percentage of albuminuria (n-11, 22.4%) compared to those with secondhand and unexposed to smoke. However, our results are not consistent with Erikson et al[24] who showed that hypertension is not associated with decreased GFR, the reasons may be not considering effects of antihypertensive drugs on BP and measurement of GFR instead of calculating eGFR from creatinine.

The overweight and obesity, a modifiable risk factors for CKD, showed statistical significant association with decreased eGFR, however, it was not significantly related to proteinuria as seen in our study. The results are consistent with Josef et al.[25] who reported a relationship of decreased eGFR and CKD in overweight and obese individuals. The kidney disorders related to obesity are considered to be secondary to glomerular hyper filtration, and release of inflammatory mediators from fat tissue. Albuminuria in obese persons is associated with large glomeruli, thickened basement membrane and podocyte distortion. The Boston University Framingham study (MESA) after 20 years of follow up, showed an association of BMI with risk of kidney disease and declared 20% increase of kidney disease with a single unit increase of BMI.[26] A study from Copenhagen involving 20,000 women and 17,000 men aged 30–80 years showed 2.0–6.0 mm Hg higher systolic and 1–3 mm Hg raised diastolic pressure for each 10% increase in BMI.[27]

Active cigarette smoking showed strong and significant association with albuminuria (22.4%), an important risk factor for progressive kidney disease. The Dialysis Mobidity and Mortality Study (DMMS) Wave 2, showed >40% patients on dialysis were smokers or secondhand smoker, but the association between smoking and decreased GFR, and albuminuria was non-significant.[28] Many studies declared that cigarette smoke causes a decrease in GFR in diabetic patients with normal

or near-normal renal function.[9,11]

In cigarette smoke there are increased serum cadmium and lead levels resulting glomerular dysfunction, while nicotine results increased incidence of micro-albuminuria leading to proteinuria and renal failure. These heavy toxins of cigarette smoke results renal damage by increased lipid peroxidation in the liver, decreased superoxide dismutase and increased catalase activity in the kidney, and stimulation of sympathetic nervous system with elevation in blood pressure. There occurs intra-renal vasoconstriction and effect on glomerular vessels which in turn stimulate renin–angiotensin–aldosterone system, however, it may be a sign of glomerular hyper-filtration and early stage renal damage that is similar as observed in diabetic nephropathy.[29,30]

Our results are in agreement with a number of studies which showed that the participants with proteinuria have decreased eGFR. The KDIGO proposed risk classification showed that people with GFR >60 ml/min/1.73 m2, are taken healthy; but they are at risk of CKD if they have albuminuria and require early management indicating the significance of proteinuria in CKD progression.[31] Yuka et al.[32] showed that most smokers generally do not show any renal deterioration during their life, except a small population who show proteinuria. The process of albuminuria occurs through induction of chemokine in tubules, infiltration of inflammatory cells in the interstitium through activation of complement system and sustained fibrogenesis.[33] Various screening programs based on proteinuria are done worldwide to find out and to reduce the dramatic increase in CKD prevalence, however, there is no evidence of benefit of these screening is seen.

CONCLUSION

Active and secondhand tobacco smoke causes an increased risk of developing proteinuria and decreased eGFR in most healthy adolescences.

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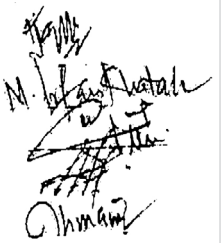
1	Ijaz Ali	Study design, Statistical analysis, Data interpretation.	
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