ORIGINAL CONTRIBUTION

A Case-control Study of Buerger's Disease

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A nation-wide case-control study was conducted to identify the risk factors and to give clues to the etiology of Buerger's disease. Cases were 153 male patients who were the receivers of national financial aids for the treatment of the disease and were enrolled in public health center. For each case, a control was randomly selected from the list of the examinees of health examinations in the public health center same as the case and was matched to the case by age (± 5 years old) and sex. Self-administered questionnaires were mailed to all study participants. The results of statistical analyses under the condition that the estimated onset age of the case was under 50 years old were as follows: (1) strong link between tobacco and Buerger's disease was statistically reconfirmed. (2) cases consumed a less amount of milk than controls. (3) cases were engaged in physical works more frequently and under noisier and dustier environments than controls. (4) the past history of allergic rhinitis was found more on the side of cases. *J Epidemiol*, 1991; 1: 19-25.

Buerger's disease, risk factors, epidemiology, a case-control study

Buerger's disease is pathologically defined as a nonatherosclerotic, segmental, inflammatory, and occlusive disease of small and medium-sized arteries and veins involving distal vessels of the upper and lower extremities.¹⁻⁵ The etiology of this disease still remains obscure, whereas numerous risk factors have been postulated.¹⁻⁹ Although recently it has been suggested that Buerger's disease is an autoimmune disorder triggered by smoking,^{2,4} its low incidence rate makes it difficult to verify this theory.

A case-control observation is considered to be a method of utility for the study of a disease with low incidence rate. The present study thus employed a nation-wide case-control study in order to identify the risk factors and to give clues to the etiology of Buerger's

disease, collecting cases through the registry in which the patients of Buerger's disease, which is one of the intractable diseases designated by the Ministry of Health and Welfare (MHW), are to enroll to receive the national financial aids for the treatment from the MHW.

MATERIALS AND METHODS

Cases were 159 patients (153 males and 6 females) in 16 prefectures (Table 1) who were registered to receive the financial aids for the treatment of Buerger's disease between April 1988 and November 1990 and who complied with our study request.

For each case, a control was recruited, matched to

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the case by age (± 5 years old) and sex, from the lists of the examinees of health examinations conducted by the same public health centers with the case. The women who came to pregnancy check-ups and the mothers of babies and infants who visited pediatric examinations were excluded because they might make the bias of study population.

A self-administered questionnaire was mailed to each study participants. The form contained about 40 questions, which were concerning ① sex, ② year and date of birth, ③ height and weight, ④ smoking habits, ⑤ alcohol consumption, ⑥ milk intake, ⑦ employment status, ⑧ medical history, ⑨ family history, ⑩ hearing and ⑪ parity. Two types of questionnaire were prepared for the case and the control, respectively. One for the case was written in the past tense to inquire the life before Buerger's disease had developed. The other for the control was in the present tense to survey the present life.

Although the questionnaire was, in principal, a self-completing one, other family members were permitted to answer the questions on behalf of the patient. Health center officers who interviewed patients were also permitted to fill in the forms, when the patients could not write by themselves because of physical handicaps.

Statistical analyses were limited to male case-control pairs due to the small number of female data and were performed under the following three conditions. First, all the pairs in this study (this condition is called "total pairs" in this report) were analysed, and then the pairs whose cases had been under 50 years old at the onset of the disease ("the pairs conditioned with onset age"). Finally, the data of the pairs whose cases were under 50 years old at the onset and underwent angiography for the final diagnosis ("the pairs conditioned with angiography") were fed into computer. The odds ratio (OR) of paired sample was calculated by means of McNemar's method. To explore the dose-response relationship between smoking and Buerger's disease, the Mantel-extension analysis was performed.

RESULTS

The number of pairs in each prefecture was shown in Table 1. The distributions of the present age of cases and controls and the onset age of cases were as indicated in Table 2. The means and the standard deviations of present age were 47.1 ± 11.43 years old and 47.3 ± 11.46 years old for cases and controls, respectively. There was no significant difference in age distribution nor in the mean of present age between the case and the control. Angiographic examination was performed in 124 (81.0%) out of 153 cases in total pairs and 93

Table 1. Numbers of case-control pairs in prefectures.

Prefecture	Male	Female	Total
Aomori	11		11
Akita	21		21
Ibaraki	6	1	7
Tochigi	15	1	16
Saitama	3		3
Tokyo	2		2
Niigata	32		32
Toyama	13		13
Ishikawa	1		1
Gifu	13		13
Osaka	1	1	2
Wakayama	22	3	25
Tottori	3		3
Okayama	1		1
Kochi	7		7
Fukuoka	2		2
Total	153	6	159

Table 2. Age distributions of cases and controls.

Age	Case		Control
	Present age	Estimated onset age	Present age
10~19	1 (0.7)	2 (1.4)	1 (0.7)
20~29	10 (6.5)	21 (14.7)	7 (4.6)
30~39	25 (16.3)	31 (21.7)	35 (22.9)
40~49	51 (33.3)	55 (38.4)	40 (26.1)
50~59	45 (29.4)	23 (16.1)	49 (32.0)
60~69	18 (11.8)	9 (6.3)	19 (12.4)
70~79	3 (2.0)	2 (1.4)	2 (1.3)
Total	153 (100.0)	143 (100.0)	153 (100.0)

Note: Present age was as of March 31, 1989, March 31, 1990, and November 30, 1990 for cases and controls enrolled in the year of 1988, 1989 and 1990, respectively. Onset age was estimated by referring to medical records. Ten cases were excluded from scoring, since their onset ages were not recorded. Figures in parentheses show percentages.

(86.1%) of 108 cases in the pairs conditioned with onset age.

OR and 95% confidence interval (CI) of exposure factors were presented in Tables 3, 4 and 5.

Of 152 cases, except one with no reply, in total pairs, 150 (98.7%) cases answered that they had or had had smoking habits. So did 107 (99.1%) out of 108 cases in the pairs conditioned with onset age and 91 (97.8%) out of 93 cases in the pairs conditioned with angiography. There were commonly two nonsmokers among the pairs under each condition.

Continuous smoking habits were significantly associated with an increasing risk of Buerger's disease, compared with nonsmoking and cessation of smoking before the onset of Buerger's disease. Because there

Table 3. Odds ratio of exposure factors. (Total Pairs)

Factor			Pair	Ca+/Con-	Ca-/Con+	OR	95% CI
Cigarette smoking habits							
at onset	yes vs no		153	51 (33.3%)	16 (10.5%)	3.19*	1.79~ 5.99
in life	yes vs no		153	27 (17.6%)	2 (1.3%)	13.50*	3.39~117.15
inhale	vs puff		120	12 (10.0%)	2 (1.7%)	6.00*	1.34~ 55.20
Alcohol							
everyday	vs not		152	36 (23.7%)	32 (21.1%)	1.13	0.68~ 1.87
drink	vs not drink		152	18 (11.8%)	13 (8.6%)	1.38	0.64~ 3.07
Milk intake							
not drink	vs drink		153	54 (35.3%)	20 (13.1%)	2.70*	1.59~ 4.76
≤ 1-2d/w	vs ≥ 3-5d/w		153	54 (35.3%)	18 (11.8%)	3.00*	1.73~ 5.44
≤ 3-5d/w	vs everyday		153	47 (30.7%)	8 (5.2%)	5.88*	2.75~ 14.40
Working status							
employed	yes vs no		153	6 (3.9%)	3 (2.0%)	2.00	0.43~ 12.36
physical work	vs desk		146	55 (37.7%)	15 (10.3%)	3.67*	2.04~ 6.99
driver	yes vs no		147	21 (14.3%)	6 (4.1%)	3.50*	1.37~ 10.60
active	yes vs no		145	46 (31.7%)	30 (20.7%)	1.53	0.95~ 2.52
night	vs daytime		145	23 (15.9%)	12 (8.3%)	1.92	0.92~ 4.23
outdoor	vs indoor		146	45 (30.8%)	19 (13.0%)	2.37*	1.36~ 4.29
dusty	yes vs no		143	40 (28.0%)	17 (11.9%)	2.35*	1.30~ 4.43
noisy	yes vs no		142	42 (29.6%)	18 (12.7%)	2.33*	1.31~ 4.31
Family history							
hypertension	no vs yes		153	34 (22.2%)	30 (19.6%)	1.13	0.67~ 1.92
cancer	yes vs no		153	27 (17.6%)	19 (12.4%)	1.42	0.76~ 2.70
diabetes mellitus	yes vs no		153	16 (10.5%)	3 (2.0%)	5.33*	1.53~ 28.56
angina pectoris	yes vs no		153	5 (3.3%)	5 (3.3%)	1.00	0.23~ 4.35
myocardial infarction	no vs yes		153	7 (4.6%)	6 (3.9%)	1.17	0.34~ 4.20
Buerger's disease	yes vs no		153	2 (1.3%)	0 (0.0%)	—	—
Consanguinity	yes vs no		148	9 (6.1%)	5 (3.4%)	1.80	0.54~ 6.84
Past history							
apoplexy	yes vs no		143	2 (1.4%)	1 (0.7%)	2.00	0.10~118.00
hypertension	yes vs no		142	16 (11.3%)	13 (9.2%)	1.23	0.56~ 2.78
diabetes mellitus	yes vs no		143	7 (4.9%)	7 (4.9%)	1.00	0.30~ 3.34
angina pectoris	no vs yes		143	3 (2.1%)	2 (1.4%)	1.50	0.17~ 17.96
myocardial infarction	yes vs no		143	2 (1.4%)	2 (1.4%)	1.00	0.07~ 13.80
asthma	no vs yes		143	4 (2.8%)	2 (1.4%)	2.00	0.29~ 22.11
allergic rhinitis	no vs yes		143	15 (10.5%)	3 (2.1%)	5.00*	1.41~ 26.94
trauma	yes vs no		152	35 (23.0%)	17 (11.2%)	2.06*	1.12~ 3.92
operation	no vs yes		153	36 (23.5%)	35 (22.9%)	1.03	0.63~ 1.69
blood transfusion	no vs yes		152	7 (4.6%)	4 (2.6%)	1.75	0.44~ 8.15
Hearing loss	yes vs no		153	14 (9.2%)	7 (4.6%)	2.00	0.76~ 5.86

Note: significance: *p<0.001, *p<0.01, *p<0.05

Ca: case, Con: control

OR: odds ratio, CI: confidence interval

was a suspicion that those who answered that they had stopped smoking before the onset of the disease actually gave up smoking after the diagnosis, however, nonsmokers were then compared with the total of ex-smokers and current smokers. OR then increased. There was also a strong dose-response relationship between Buerger's disease and Brinkman index (Tables 6, 7 and 8).

Alcohol consumption had no association with Buer-

ger's disease.

Less intake of milk was found to be statistically associated with Buerger's disease as shown in Tables 3, 4 and 5.

OR of physical work for Buerger's disease was significantly higher than that of desk work. Noisy and dusty working environment were also statistically significant risk factors.

Family history of diabetes mellitus (DM) was stat-

Table 4. Odds ratio of exposure factors. (Estimated onset age under 50 years old)

Factor		Pair	Ca+/Con-	Ca-/Con+	OR	95% CI
Cigarette smoking habits						
at onset	yes vs no	109	35 (32.1%)	9 (8.3%)	3.89 ^a	1.83~ 9.20
in life	yes vs no	109	21 (19.3%)	2 (1.8%)	10.50 ^a	2.57~ 92.37
inhale	vs puff	83	5 (6.0%)	0 (0.0%)	—	—
Alcohol						
everyday	vs not	108	23 (21.3%)	21 (19.4%)	1.10	0.58~ 2.08
drink	vs not drink	108	10 (9.3%)	9 (8.3%)	1.11	0.41~ 3.09
Milk intake						
not drink	vs drink	109	37 (33.9%)	14 (12.8%)	2.64 ^b	1.40~ 5.29
≤1-2d/w	vs ≥3-5d/w	109	37 (33.9%)	14 (12.8%)	2.64 ^b	1.40~ 5.29
≤3-5d/w	vs everyday	109	30 (27.5%)	6 (5.5%)	5.00 ^a	2.05~ 14.69
Working status						
employed	yes vs no	109	4 (3.7%)	3 (2.8%)	1.33	0.23~ 9.10
physical work	vs desk	103	36 (35.0%)	12 (11.7%)	3.00 ^a	1.53~ 6.33
driver	yes vs no	105	14 (13.3%)	3 (2.9%)	4.67 ^c	1.30~ 25.33
active	yes vs no	102	32 (31.4%)	21 (20.6%)	1.52	0.85~ 2.78
night	vs daytime	102	18 (17.6%)	9 (8.8%)	2.00	0.85~ 5.05
outdoor	vs indoor	103	30 (29.1%)	14 (13.6%)	2.14 ^c	1.10~ 4.37
dusty	yes vs no	102	31 (30.4%)	13 (12.7%)	2.38 ^c	1.21~ 4.96
noisy	yes vs no	102	31 (30.4%)	12 (11.8%)	2.58 ^b	1.29~ 5.52
Family history						
hypertension	no vs yes	109	28 (25.7%)	20 (18.3%)	1.40	0.76~ 2.62
cancer	yes vs no	109	19 (17.4%)	13 (11.9%)	1.46	0.68~ 3.22
diabetes mellitus	yes vs no	109	12 (11.0%)	0 (0.0%)	—	—
angina pectoris	no vs yes	109	5 (4.6%)	3 (2.8%)	1.67	0.32~ 10.73
myocardial infarction	no vs yes	109	4 (3.7%)	4 (3.7%)	1.00	0.19~ 5.37
Buerger's disease	yes vs no	109	2 (1.8%)	0 (0.0%)	—	—
Consanguinity	yes vs no	106	8 (7.5%)	5 (4.7%)	1.60	0.46~ 6.22
Past history						
apoplexy	yes vs no	101	1 (1.0%)	0 (0.0%)	—	—
hypertension	no vs yes	101	12 (11.9%)	10 (9.9%)	1.20	0.48~ 3.10
diabetes mellitus	yes vs no	101	4 (4.0%)	3 (3.0%)	1.33	0.23~ 9.10
angina pectoris	yes vs no	101	2 (2.0%)	1 (1.0%)	2.00	0.10~ 118.00
myocardial infarction	yes vs no	101	1 (1.0%)	0 (0.0%)	—	—
asthma	no vs yes	101	2 (2.0%)	1 (1.0%)	2.00	0.10~ 118.00
allergic rhinitis	no vs yes	101	12 (11.9%)	2 (2.0%)	6.00 ^c	1.34~ 55.20
trauma	yes vs no	109	20 (18.3%)	14 (12.8%)	1.43	0.69~ 3.06
operation	no vs yes	109	28 (25.7%)	24 (22.0%)	1.17	0.65~ 2.10
blood transfusion	no vs yes	109	2 (1.8%)	1 (0.9%)	2.00	0.10~ 118.00
Hearing loss	yes vs no	109	11 (10.1%)	5 (4.6%)	2.20	0.70~ 8.08

Note) significance: ^ap<0.001, ^bp<0.01, ^cp<0.05

Ca: case, Con: control

OR: odds ratio, CI: confidence interval

istically associated with Buerger's disease only in total pairs. Among the pairs conditioned with onset age and the pairs conditioned with angiography, there was

no case with the family history of DM.

The past history of allergic rhinitis significantly increased the risk of Buerger's disease.

Table 5. Odds ratio of exposure factors. (Estimated onset age under 50 years old & angiography performed)

Factor		Pair	Ca+/Con-	Ca-/Con+	OR	95% CI
Cigarette smoking habits						
at onset	yes vs no	93	30 (32.3%)	8 (8.6%)	3.75*	1.68~ 9.47
in life	yes vs no	93	16 (17.2%)	2 (2.2%)	8.00*	1.88~ 71.72
inhale	vs puff	73	4 (5.5%)	0 (0.0%)	—	—
Alcohol						
everyday	vs not	93	21 (22.6%)	19 (20.4%)	1.11	0.57~ 2.17
drink	vs not drink	93	17 (18.3%)	15 (16.1%)	1.13	0.53~ 2.44
Milk intake						
not drink	vs drink	93	30 (32.3%)	11 (11.8%)	2.73*	1.33~ 6.03
≤1-2d/w	vs ≥3-5d/w	93	29 (31.2%)	10 (10.8%)	2.90*	1.37~ 6.67
≤3-5d/w	vs everyday	93	25 (26.9%)	5 (5.4%)	5.00*	1.88~ 16.72
Working status						
employed	yes vs no	93	4 (4.3%)	1 (1.1%)	4.00	0.40~196.99
physical work	vs desk	88	29 (33.0%)	11 (12.5%)	2.64*	1.28~ 5.85
driver	yes vs no	91	11 (12.1%)	3 (3.3%)	3.67	0.97~ 20.47
active	yes vs no	88	27 (30.7%)	20 (22.7%)	1.35	0.73~ 2.54
night	vs daytime	88	15 (17.0%)	8 (9.1%)	1.88	0.75~ 5.11
outdoor	vs indoor	88	24 (27.3%)	12 (13.6%)	2.00	0.96~ 4.39
dusty	yes vs no	87	26 (29.9%)	11 (12.6%)	2.36*	1.13~ 5.30
noisy	yes vs no	87	26 (29.9%)	10 (11.5%)	2.60*	1.21~ 6.04
Family history						
hypertension	no vs yes	93	23 (24.7%)	16 (17.2%)	1.44	0.73~ 2.91
cancer	yes vs no	93	16 (17.2%)	12 (12.9%)	1.33	0.59~ 3.09
diabetes mellitus	yes vs no	93	11 (11.8%)	0 (0.0%)	—	—
angina pectoris	no vs yes	93	3 (3.2%)	2 (2.2%)	1.50	0.17~ 17.96
myocardial infarction	yes vs no	93	4 (4.3%)	3 (3.2%)	1.33	0.23~ 9.10
Buerger's disease	yes vs no	93	2 (2.2%)	0 (0.0%)	—	—
Consanguinity	yes vs no	91	7 (7.7%)	4 (4.4%)	1.75	0.44~ 8.15
Past history						
apoplexy	yes vs no	85	1 (1.2%)	0 (0.0%)	—	—
hypertension	no vs yes	85	10 (11.8%)	9 (10.6%)	1.11	0.41~ 3.09
diabetes mellitus	yes vs no	85	4 (4.7%)	2 (2.4%)	2.00	0.29~ 22.11
angina pectoris	yes vs no	85	2 (2.4%)	1 (1.2%)	2.00	0.10~118.00
myocardial infarction	yes vs no	85	1 (1.2%)	0 (0.0%)	—	—
asthma	no vs yes	85	2 (2.4%)	1 (1.2%)	2.00	0.10~118.00
allergic rhinitis	no vs yes	85	11 (12.9%)	1 (1.2%)	11.00*	1.60~473.47
trauma	yes vs no	93	20 (21.5%)	11 (11.8%)	1.82	0.83~ 4.20
operation	yes vs no	93	22 (23.7%)	21 (22.6%)	1.05	0.55~ 2.00
blood transfusion	yes vs no	93	2 (2.2%)	0 (0.0%)	—	—
Hearing loss	yes vs no	93	10 (10.8%)	5 (5.4%)	2.00	0.62~ 7.46

Note) significance: *p<0.001, *p<0.01, *p<0.05

Ca: case, Con: control

OR: odds ratio, CI: confidence interval

DISCUSSION

Previous epidemiological studies indicated that Buerger's disease predominantly affected men and that it rarely occurred in women.¹⁻⁴⁾ The reported proportion of women with Buerger's disease was commonly within the range of 0~5%.^{1-4,8,10)} In the present series, 6 (3.8%) out of 159 patients were women. Among

them, four patients were smokers and 2 were non-smokers. Recently the increase in the incidence of women with Buerger's disease has been disclosed,^{1,10)} which paralleled the increase of female smokers in number.¹⁾ Smoking was here again strongly suggested to be a risk factor of Buerger's disease. And the higher incidence of nonsmokers in female patients¹⁾ suggests the possible involvement of passive smoking in the etiology of Buerger's disease.⁹⁾ Our statistical

Table 6. Dose-response relation between smoking index and Buerger's disease. (Analysis of total cases)

B.I.	Case	Control	Total	Cum. Freq.	R.R.	Significance
< 0 >	2 (1.3)	27 (17.8)	29	0.0493	1.0000	—
<1 -400>	58 (38.2)	57 (37.5)	115	0.2862	13.7368	p<0.001
<401-800>	59 (38.8)	47 (30.9)	106	0.6497	16.9468	p<0.001
<801- >	33 (21.7)	21 (13.8)	54	0.9128	21.2143	p<0.001
Total	152 (100.0)	152 (100.0)	304	—	—	—

$\chi^2=13.9012$ by Mantel-extension method ($p=0.000193$)

Note) B.I.: Brinkman index, Cum. Freq.: cumulative frequency, R.R.: relative risk

Figures in parentheses show percentages.

Table 7. Dose-response relation between smoking index and Buerger's disease. (Analysis of cases whose estimated onset ages were under 50 years old)

B.I.	Case	Control	Total	Cum. Freq.	R.R.	Significance
< 0 >	2 (1.8)	21 (19.3)	23	0.0550	1.0000	—
<1 -400>	47 (43.2)	45 (41.3)	92	0.3188	10.9667	p<0.001
<401-800>	41 (37.6)	31 (28.4)	72	0.6950	13.8871	p<0.001
<801- >	19 (17.4)	12 (11.0)	31	0.9312	16.6250	p<0.001
Total	109 (100.0)	109 (100.0)	218	—	—	—

$\chi^2=10.5624$ by Mantel-extension method ($p=0.001154$)

Note) B.I.: Brinkman index, Cum. Freq.: cumulative frequency, R.R.: relative risk

Figures in parentheses show percentages.

Table 8. Dose-response relation between smoking index and Buerger's disease. (Analysis of cases with angiography, whose estimated ages were under 50 years old)

B.I.	Case	Total	Cum. Freq.	R.R.	Significance
< 0 >	2 (2.2)	16 (17.2)	18	0.0511	1.0000
<1 -400>	37 (39.7)	40 (43.0)	77	0.3065	7.4000
<401-800>	36 (38.7)	28 (30.1)	64	0.6855	10.2857
<801- >	18 (19.4)	9 (9.7)	27	0.9301	16.0000
Total	93 (100.0)	93 (100.0)	186	—	—

$\chi^2=10.8362$ by Mantel-extension method ($p=0.000995$)

Note) B.I.: Brinkman index, Cum. Freq.: cumulative frequency, R.R.: relative risk

Figures in parentheses show percentages.

analyses were done under 3 conditions separately. The phrase of "under 50 years old at the onset" was derived from the diagnostic criteria for Buerger's disease recommended by the MHW⁽¹¹⁾ and the majority of the literature supported this condition^(2,4,7,8,11,12) because atherosclerosis, which is often diagnosed as Buerger's disease, increases in frequency among patients over 50 years old. Angiography is said to refine the diagnosis⁽²⁾ although it is not included in the diagnostic criteria.

In our study, Buerger's disease was proved to be statistically associated with several exposure factors. The exposure factors which had significant odds ratios even when analyses were done most strictly conditioned with both the onset age and angiography were ① smoking status, ② less intake of milk, ③ physical

work, ④ noisy working environment, ⑤ dusty working environment, and ⑥ the past history of allergic rhinitis.

It is well established that smoking is deeply related to the exacerbation and remission of Buerger's disease^(2,4,5,7) and that habitual smoking is a strong determinant of a risk to the disease.^(1,3-5,7-9) Strong link between smoking habits and Buerger's disease was here reconfirmed.

Answers to questionnaires, however, are often considered not to be objective, because they are made by patients themselves. The fact that there were two would-be nonsmokers among cases made it clearer that the assessment of smoking status should be done with more objective indicators. To acquire more reliable information concerning smoking habits, some biologi-

cal parameters are recommended.^{1,3,41} Among them, cotinine, a derivative of nicotine, has been said to be a better index of smoking evidence. Urinary cotinine of smokers were significantly higher than that of nonsmokers.¹² The test of biological parameters will be of necessity to know not only whether a patient smoked or not but also whether he or she suffered from passive smoking or not.^{2,12)}

Our finding on milk intake contradicted that of the previous report in which patients drank more milk than controls.¹³⁾ The biological significance of milk intake remains unclear.

On the other hand, employment status may play a role in the etiology of Buerger's disease.¹³⁾ Allergic rhinitis as a risk factor of Buerger's disease has not yet been reported as far as we know.

Before making a conclusion on risk factors, the potential confounding factors that might disguise the statistic results should be evaluated. In addition, the accumulation of data will be necessary. At present, smoking seems to solely gain universal acceptance as a risk factor of Buerger's disease among statistically significant risk factors proven in the present study. To assess whether or not a factor is actually involved in the development of Buerger's disease is such a tough task that the epidemiological study should be pursued in future and that biological methods should also be introduced to give epidemiological findings the etiological guarantee.

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