1	<b>Risk Factors Associated with Dengue Virus Infection</b>
2	in Guangdong Province: a Community-based Case-control
3	Study
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15	Abstract
16	Background:
17	Dengue fever is a mosquito-borne infectious disease, and it is now still epidemic in China,
18	especially in Guangdong Province. Owing to the absence of dengue vaccination, effective
19	preventive measure is critical for controlling of dengue fever. This study aimed to explore
20	the individual risk factors of dengue virus infection in Guangdong Province, as well as to
21	provide a scientific basis for prevention and supervision of dengue fever in future.
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**Methods:** 

A case-control study including 237 cases and 237 controls was performed. The data was collected from the epidemiological questionnaires. Univariate analysis was used for preliminary screening of 28 variables potentially related to dengue virus infection, and an unconditioned logistic regression analysis was used for multivariate analysis to analysis those statistically significant variables.

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## 30 **Results:**

Multivariate analysis of the result showed three independent risk factors: activities in the park (odd ratio [OR]= 1.70, 95%CI 1.03 to 2.83), outdoor sports (OR= 1.67, 95%CI 1.07 to 2.62), and poor indoor daylight quality (OR= 2.27, 95%CI 1.00 to 5.15); and two protective factors: two persons per room (OR=0.43, 95%CI 0.28 to 0.67), three persons and above per room (OR=0.43, 95%CI 0.22 to 0.86), using air-condition (OR=0.43, 95%CI 0.20 to 0.93).

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# 37 Conclusion:

These results are conducive to learn the risk factors for dengue virus infection in Guangdong Province. It is crucial to provide effective and efficient strategy to improve environmental protection and anti-mosquito measures. In addition, more systematic studies are needed to explore the other potential risk factors for dengue fever infection.

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## 43 Key words:

44 Dengue fever; Infection; Risk factors; Case-control study; Logistic regression analysis

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#### 46 Author summary

47 Dengue fever, one of the mosquito-borne infectious diseases, is mainly transmitted by Aedes 48 aegypti in Asia and Southeast Asia countries. Since 1978, the incidence of dengue fever has 49 markedly increased in China especially in Guangdong province. In order to formulate the

50 effective prevention and control measures, we explored the risk factors of dengue virus 51 infection in Guangdong Province by conducting a case-control study. In this study, 237 52 patients with dengue virus infection and 237 participants without dengue virus infection 53 were included. Then through these questionnaires and data analysis, we found that activities in the park, outdoor sports, and poor indoor daylight quality significantly contributed to the 54 residents' risk of dengue virus infection. On the other hand, we observed that using 55 air-condition and using anti-mosquito measures were effective personal prevention 56 57 interventions.

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# 59 Introduction

60 Dengue fever (DF) is an acute viral disease caused by four distinct serotype dengue virus, 61 transmitted between humans by Aedes aegypti. In endemic countries in Asia and America, the burden of dengue is approximately 1,300 disability-adjusted life years (DALYs) per 62 63 million populations, which is comparable to the disease burden of other childhood and 64 tropical diseases, including tuberculosis, in these regions [1]. In Asia, epidemic dengue 65 haemorrhagic fever (DHF) has expanded geographically from southeast Asian countries west to India, Sri Lanka, the Maldives, and Pakistan and then east to China [1]. According to the 66 World Health Organization (WHO) statistics, there were only nine countries experiencing 67 severe dengue epidemics before 1970. However, the number of countries which have 68 experienced the disease now is more than 100, and the actual number of dengue infection is 69 70 approximately 390 million, of which 500, 000 people require hospital admission because of 71 severe dengue [2].

In 1978, the first reported DF outbreak due to Dengue virus (DENV) type 4 occurred in Foshan (adjacent to Guangzhou), a city in Guangdong Province, from where the spread of DF started in the southern provinces of China [3]. The DF incidence in Guangdong Province has been the highest in mainland China during the past decades, accounting for more than 65% of all cases in the country [4]. Besides, in 2013, total 4,662 cases occurred in mainland China, 62.08% of which were in Guangdong province. And the number of dengue fever cases increased dramatically to 48,162 in mainland China in 2014, 93.83% of these cases

79 were reported from Guangdong province [5]. Thus, it is urgent to control the outbreak of 80 dengue fever in Guangdong, which can serve as a bridge to transmit DF to other provinces in 81 mainland China. Unfortunately, there are no effective drugs and vaccine to treat or prevent 82 dengue fever so far.

83 In order to effectively prevent dengue fever, understanding the infection risk factors for 84 dengue fever is necessary. Now, it is clear that the rapid growth of population, urbanization, 85 and convenient modern transportation have greatly increased the spread of dengue fever [6]. 86 However, most of the current case-control studies on risk factors are associated with sever 87 dengue such as dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) and the 88 variables are all related to clinical and laboratory indexes [7-10]. In addition, with the development of the primary healthcare, some researchers were interested in exploring the 89 90 positive effect of community participation in diminishing favorable household environments 91 of dengue vectors [11:12]. Besides, environmental factors, awareness and knowledge of 92 dengue prevention were also responsible for a significant reduction in dengue transmission 93 [13-14]. To explore the dengue infection risk factors in Guangdong and provide basis for 94 formulating control strategies in Guangdong province, several macroscopically descriptive 95 studies were carried out, which provided more information on group level as well as climate 96 factors, but less information on personal protective measures [15,16]. In order to get more 97 related information of risk factors on individual level and provide more specific prevention 98 approaches, this case-control study was conducted. Geographically, Guangzhou city and 99 Zhongshan city are located in the Pearl River Delta Region of Guangdong, which is the main area where dengue fever epidemics highly [17,18], meanwhile, Guangzhou city is the capital 100 101 of Guangdong province and the first reported case of autochthonous dengue fever occurred 102 in Zhongshan city [19]. Thus, the prevalence of dengue fever in Guangzhou city and 103 Zhongshan city is a good representation of Guangdong's. The cases and controls, which 104 were selected from the communities in Guangzhou city and Zhongshan city, were identified 105 based on serum test of dengue virus IgG and IgM. The potential risk factors analyzed 106 included personal life activities, personal hygiene habits, housing situation, living 107 environment, mosquito protection status and residential surroundings.

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#### 109 Methods

# 110 Samples collection

111 The case-control study was performed based on the project of Research on Prevention and Control of Human Immunodeficiency Virus and Hepatitis B Virus in Guangdong province 112 113 which has a 200,000-sample database. The demographic information of the database could 114 be seen in our related study [20]. Totally, 3,136 serum samples were selected from residents 115 of Yuexiu District in Guangzhou city (699), Liwan District in Guangzhou city (1386), Torch 116 Development Area in Zhongshan City (180) and Xiaolan Town in Zhongshan city (1051) 117 respectively via stratified cluster sampling rooted in the database for serological testing. That 118 is, approximate 30 to 35 persons a month were sampled from every age group (under 19 119 years group, 19 to 40 years group, 41 to 65 years group, and over 65 years group) during two years from September 2013 to August 2015. 120

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# 122 Enzyme Immunoassay Test

The enzyme-linked immunosorbent assay (ELISA) was used to detect dengue antibody IgG and IgM. The IgG antibody was measured by indirect ELISA (LOT: 01P20A006, Inverness Medical/Panbio Australia), whereas the antibody of dengue IgM was tested via capture ELISA (LOT:01P30A002, Inverness Medical/Panbio Australia). The undefined results were confirmed by the colloidal gold method (LOT: DEN141001, Inverness Medical/Cortez USA). The detail could be found in the relevant study [20].

# 129 Ethical Statement

The work obtained the ethics approval from the Institutional Review Board of the School of Public Health at the Sun Yat-sen University (L2017030), in line with the guidelines to protect human subjects. After understanding the research objective and being ensured that their personal information can keep private, all research subjects or the guardians signed the

written informed consents. And every of the participants had the right to withdrawal fromthis study at any time.

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## 137 Case definition and selection of control

Among the 3,136 serum samples, the number of individuals detected as IgG antibody positive and IgM antibody positive were 305 and 103 respectively, 34 of which were positive for both antibodies. Thus 374 antibody-positive samples were defined as dengue infection and those willing to receive questionnaire survey were chosen as members of the case group.

In this study, 256 dengue infections were chosen to fill in the questionnaires, however, 143 19 questionnaires with missing most of important information were eliminated. Eventually, 144 237 infections were included in the case group. There was no statistical difference in gender 145 between the persons who were willing to receive questionnaire survey and those who were 146 unwilling (p=0.950>0.05), as well as in age (p=0.127>0.05).

The controls were selected from those who were tested negative both to IgG and IgM using frequency matching. That is, the candidate controls were stratified according to the age and sex ratio of the case group, and selected by convenience sampling (participants volunteered to be part of the samples) from each layer. In total, 308 questionnaires were completed by the persons whose IgG and IgM antibodies were both negative. To enhance the comparability of the study, according to the community information of the 237 cases, a further match was done and 237 controls were selected.

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#### 155 Data collection and analysis

The phone questionnaire was carried out by these trained investigators to obtain the information strictly according to the facts, then some subjects were interviewed face to face to verify the validity of their information. The main contents of the questionnaire included: general demographic characteristics (age, gender, blood type, average household income) ; personal life activities, such as activities in the park, outdoor sports (such as hiking, 161 mountain climbing and camping) and outbound tourism experience; personal hygiene habits 162 (domestic sewage and garbage management, participate in the community hygiene 163 management intervention); housing situation, like the age and area of inhabitation and living 164 floor; living condition (average numbers of person per room, use of air conditioning, indoor 165 daylight quality, animals or aquatic plants on property, etc.); mosquito protection status (use 166 of mosquito nets, pesticide, etc.); residential surroundings (whether there are junk yards, 167 ponds or construction sites within 200 meters).

- Epidata3.1 software was used to establish a database of individual risk factors for dengue infection among residents in Guangdong Province. All the data were analyzed by SPSS statistics 23.0 software. A univariate analysis was applied for preliminary screening of variables, and there would be an unconditioned logistic regression analysis method for multivariate analysis to analysis those statistically significant variables.
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#### 174 **Results**

# 175 General demographic characteristics of the samples

In total, 474 subjects were recruited successfully, including 237 cases and 237 controls. The
gender ratio was 1:1.66 (male: female) in both the case group and the control group. The
potential confounders were comparable between the two groups (Table 1).

 Table 1
 The demographic characteristics of cases and controls

Demographic characteristics <sup>a</sup>	Cases (N/%) (n= 237)	Controls (N/%) (n= 237)	<i>p</i> -value
Age (mean± SD)	63.1±22.1	$61.2 \pm 21.3$	0.330
Gender			—
Male	89 (37.55)	89 (37.55)	
Female	148 (62.45)	148 (62.45)	
Residence			0.157
Permanent residents	225 (94.94)	231 (97.47)	
Floating population <sup>b</sup>	12 (5.06)	6 (2.53)	
Household residents			0.400
1	27 (11.39)	17 (7.17)	
2-3	126 (53.16)	125 (52.75)	

4-5	75 (31.65)	84 (35.44)	
>6	9 (3.80)	11 (4.64)	
Per capita family income monthly			0.320
(¥)			
<2000	50 (21.10)	36 (15.19)	
2000-4999	145 (61.18)	162 (68.35)	
5000-7999	35 (14.77)	31 (13.08)	
>=8000	7 (2.95)	8 (3.38)	
Blood type			0.202
А	18 (7.59)	14 (5.91)	
В	15 (6.33)	19 (8.02)	
0	29 (12.24)	46 (19.40)	
AB	9 (3.80)	6 (2.53)	
Unknown	166 (70.04)	152 (64.14)	

<sup>a</sup> Except where otherwise indicated, values are the number (percentage) of patients with the
 characteristic. <sup>b</sup> Floating population refers to migrants without local household registration
 status.

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# 184 Univariate analysis

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Total 28 potential risk factors were analyzed, which were further divided into six dimensions, 186 187 which were personal life activities, personal hygiene habits, housing situation, living 188 conditions, mosquito protection status and residential surroundings respectively. Just as shown in Table2, people who with activities in the park had a significantly higher risk of 189 190 getting dengue virus infection than those who without activities in the park (p=0.049<0.05). 191 Significantly, people who had outdoor sports were more likely to be infected by the dengue 192 fever virus compared with those who had no outdoor sports (p=0.009<0.05). At the same time, 193 there were statistical difference on housing type (p=0.040<0.05), the average numbers of 194 person per room (p=0.000 < 0.05), using air-condition (p=0.026 < 0.05) and the indoor daylight 195 quality (p=0.032 < 0.05) between the case group and the control group.

But rather, for the factors of residential surroundings within 200 meters, there were no statistical difference on the existence of garbage collection sites, junk yards, ponds, and construction sites.

	Cases (N/%) (n=237)	Controls (N/% (n=237)	%)OR (95% CI)	<i>p</i> -value
Contacting with dengue fever patients	[			0.655
Yes	3 (1.27)	2 (0.84)	1.51 (0.25, 9.10)	)
No	234 (98.73)	235 (99.16)	Reference	
Outbound tourism experience	2			0.867
Yes	19 (8.02)	20 (8.44)	Reference	
No	218 (91.98)	217 (91.56)	1.06 (0.55, 2.04	)
Activities in the park				0.049*
Yes <sup>#1</sup>	200 (84.39)	183(77.22)	1.60 (1.00, 2.54)	)
No	37 (15.61)	54 (22.78)	Reference	
Outdoor sports				0.009*
Yes <sup>#2</sup>	74 (31.22)	49 (20.68)	1.74 (1.15, 2.64)	)
No	163 (68.78)	188 (79.32)	Reference	
Domestic sewage disposal frequency				0.655
Everyday	125 (52.74)	118 (49.79)	Reference	
Two day	25 (10.55)	20 (8.44)	1.18 (0.62, 2.24)	)
Three day and above	35 (14.77)	42 (17.72)	0.79 (0.47, 1.32)	)
No domestic sewage	52 (21.94)	57 (24.05)	0.86 (0.55, 1.35)	)
Garbage disposal frequency				0.311
Everyday	223 (94.09)	228 (96.20)	Reference	
Two day	11 (4.64)	5 (2.11)	2.25 (0.77, 6.58)	)
Three day and above	3 (1.69)	4 (1.69)	0.77 (0.17, 3.47)	)

Table 2 Univariate analysis of risk factors for dengue virus infection

Participate in the community				0.104
hygiene management intervention				
Yes	77 (32.49)	94 (39.66)	Reference	
No	· /	143 (60.34)	1.37 (0.94, 1.99)	
Location	~ /	~ /		0.061
Rural	15 (6.33)	11 (4.64)	0.34 (0.08, 1.51)	
City	210 (88.61)	223 (94.09)	0.24 (0.07, 0.85)	
Urban-rural integration	12 (5.06)	3 (1.27)	Reference	
Housing building structure				0.871
Brick-wood structure	2 (0.84)	3 (1.27)	0.67 (0.11, 4.05)	
Brick-wood and concrete structure	31 (13.08)	29 (12.24)	1.07 (0.63, 1.85)	
Concrete structure	204 (86.08)	205 (86.49)	Reference	
Housing type				0.040*
Single-family apartment	60 (25.32)	39 (16.46)	Reference	
Commercial residential community	173 (73.00)	196 (82.70)	0.57 (0.37, 0.90)	
Villa	4 (1.68)	2 (0.84)	1.30 (0.23, 7.44)	
The age of the housing (year)	1			0.919
<10	23 (9.71)	24 (10.13)	Reference	
10-20	115 (48.52)	116 (48.95)	1.03 (0.54, 1.94)	
20-40	88 (37.13)	89 (37.55)	1.03 (0.54, 1.96)	
>40	11 (4.64)	8 (3.37)	1.43 (0.49, 4.21)	
Living floor				0.096
1-3	110 (46.41)	87 (36.71)	Reference	
4-9	103 (43.46)	124 (52.32)	0.66 (0.45, 0.96)	
>=10	24 (10.13)	26 (10.97)	0.73 (0.39, 1.36)	
Average numbers of person				0.000*
per room 1	91 (38.40)	51 (21.52)	Reference	

2	123 (51.90)	160 (67.51)	0.43 (0.28, 0.65)	)
>=3	23 (9.70)	26 (10.97)	0.50 (0.26, 0.96)	)
The area of housing (m <sup>2</sup> )				0.235
<50	63 (26.58)	52 (21.9)	Reference	
51-100	150 (63.29)	169 (71.31)	0.73 (0.18, 1.12)	)
101-150	19 (8.02)	11 (4.64)	1.43 (0.62, 3.26)	)
>150	5 (2.11)	5 (2.11)	0.83 (0.23, 3.01)	)
Using air-condition				0.013*
Never	26 (10.97)	11 (4.64)	Reference	
Yes	211(89.03)	226 (95.36)	0.40 (0.19, 0.82)	)
Indoor daylight quality				0.032*
Good <sup>#3</sup>	215 (90.72)	227 (95.78)	Reference	
Poor	22 (9.28)	10 (4.22)	2.32 (1.08, 5.02)	)
Ventilation effect				0.324
Good <sup>#4</sup>	221 (93.25)	226 (95.36)	Reference	
Bad	16 (6.75)	11 (4.64)	1.49(0.68, 3.28)	
Keeping pets				0.800
Yes	38 (16.03)	36 (15.19)	Reference	
No	199 (83.97)	201 (84.81)	0.94 (0.57, 1.54)	)
Raising poultry				0.589
Yes	6 (2.53)	8 (3.38)	0.74 (0.25, 2.18)	)
No	231 (97.47)	229 (96.62)	Reference	
Breeding aquatic plants				0.578
Yes	54 (20.68)	49 (20.68)	Reference	
No	183 (77.22)	188 (79.32)	0.88 (0.57, 1.37)	)
Using mosquito nets				0.361
Yes	185 (78.06)	193 (81.43)	Reference	
No	52 (21.94)	44 (18.57)	1.23 (0.79, 1.93)	)
Using mosquito repellent				0.212
Never	122 (51.48)	116 (48.95)	Reference	

Occasionally	88 (37.13)	103 (43.46)	0.81 (0.56, 1.19)	)
Often	27 (11.39)	18 (7.59)	1.43 (0.75, 2.73)	)
Using electronic mosquito				0.150
killing facilities				
Never	152 (64.14)	143 (60.34)	Reference	
Occasionally	57 (24.05)	74 (31.22)	0.73 (0.48, 1.10)	)
Often	28 (11.81)	20 (8.44)	1.32 (0.71, 2.44)	)
Using camphor				0.649
Never	177 (74.68)	168 (70.89)	Reference	
Occasionally	42 (17.72)	48 (20.25)	0.83 (0.52, 1.32)	)
Often	18 (7.60)	21 (8.86)	0.81 (0.42, 1.58)	)
The existence of garbage collection sites within 200m around housing				0.681
Yes	32 (13.50)	29 (12.24)	1.12 (0.65, 1.92)	1
No	205 (86.50)	208 (87.76)	Reference	
The existence of junk yards within 200m around housing				0.570
Yes	1 (0.42)	2 (0.84)	0.50 (0.05, 5.53)	)
No	236 (99.58)	235 (99.16)	Reference	
The existence of ponds within 200m around housing	1			0.426
Yes	45 (18.99)	52 (21.94)	0.83 (0.53, 1.30)	1
No	192 (81.01)	185 (78.06)	Reference	
The existence of construction sites within 200m around housing				0.639
Yes	24 (10.13)	21 (8.86)	1.16 (0.63, 2.15)	)
No	213 (89.87)	216 (91.14)	Reference	

201 \* Significance difference: *p*-value is less than 0.05.

202 <sup>#1</sup> Definition of Actives in the park: at least two times per week and more than half an hour one

203 time.

<sup>#2</sup> Definition of Having outdoor sports at least twice a year and more than half an hour one time.

<sup>#3</sup> Definition of Good Indoor daylight quality: The minimum requirement for sunshine in general

206 residences is not less than 2 hours in the great cold day.

<sup>#4</sup> Definition of Good Ventilation effect: The ventilation opening area of a house is not less than
5% of the floor area.

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## 210 Multivariate analysis

211 Through the univariate analysis above, there were statistical significance on six variables 212 between the case group and the control group (p values are all less than 0.05). To further analyze 213 the relative importance of the six various factors associated with dengue infection, they were all 214 brought into a multivariate model. In the unconditioned logistic regression model, activities in the 215 park, outdoor sports and the poor indoor daylight quality were significantly associated with increasing risk of dengue virus infection, with odd ratios (ORs) of 1.70, 1.67, and 2.27 216 217 respectively. On the other hand, two persons per room (OR=0.43), three persons and above per 218 room (OR=0.43) and using air-condition occasionally (OR=0.43) were significantly associated with protections against dengue virus infection (Table 3). The equation obtained by unconditional 219 logistic regression is: ln (Odds) =  $1.193 + 0.533 X_1 + 0.515 X_2 - 0.835 X_3^a - 0.835 X_3^b - 0.837 X_5 + 0.83$ 220 221 0.822 X<sub>6</sub>. X<sub>1</sub> presents park experience, X<sub>2</sub> presents outdoor sports,  $X_3^a$  presents two persons per room, X<sub>3</sub><sup>b</sup> presents three persons and above per room, X<sub>5</sub> presents using air-condition and X<sub>6</sub> 222 223 presents the poor indoor daylight quality.

 Table 3
 Multivariate analysis on risk factors for dengue virus infection

Risk factors	В	Odd Ratio (95% CI)	<i>p</i> -value
Activities in the park			0.039*
Yes	0.533	1.70 (1.03, 2.83)	
No		Reference	
Outdoor sports			0.024*
Yes	0.515	1.67 (1.07, 2.62)	
No		Reference	
Housing type			0.056
Single-family apartment		Reference	
Commercial residential district	-0.571	0.57 (0.35, 0.91)	
Villa	0.057	1.06 (0.16, 6.94)	
Average numbers of person per room			0.000*
1		Reference	
2	-0.835	0.43 (0.28, 0.67)	
>=3	-0.835	0.43 (0.22, 0.86)	
Using air-condition			0.032*
Never		Reference	

Yes	-0.837	0.43 (0.20, 0.93)	
Indoor daylight quality			0.044*
Good		Reference	
Poor	0.822	2.27 (1.00, 5.15)	
Constant	1.193	3.296	0.009

# \*Significance difference where *p*-value is less than 0.05.

226

# 227 Discussion

Our study showed that activities in the park, outdoor sports and the poor indoor daylight quality significantly increased the 1.70-time, 1.67-time, and 2.27-time risk of developing dengue infection respectively in Guangdong Province. In addition, it also suggested that more than one person per room and using air-condition might decrease the risk for dengue virus infection by close to 0.43 times.

233 The result of the study revealed that people with activities in the park have significantly 234 higher risk of contracting dengue fever than those with no activities in the park. This could be 235 related to the high density of the mosquito of Aedes albopictus in the park [21]. And when 236 playing in the park especially in the morning and at dusk, residents were usually casually 237 dressed with more skin exposed, which made it easier to be bitten by mosquitoes and increased the risk of dengue infection. Besides, research showed that the main protocols of 238 239 mosquito prevention were using mosquito nets, pesticide and mosquito repellent, but less 240 residents tend to use mosquito repellent outdoor [22]. Thus it is necessary for residents to 241 increase the awareness of adopting some approaches to prevent mosquito in their daily lives 242 and reduce the risk of dengue fever. For instance, wearing long-sleeve clothes during 243 activities in the park. Meanwhile, having outdoor sports was another risk factor for dengue 244 virus infection, the explanation for which might be that the forest margin, the holes of trees 245 and the natural reservoirs were the origins of Aedes albopictus. Simultaneously, these places 246 were good choices for residents to hike and go camping [23]. Therefore, outdoor sports 247 increased the risk of mosquito bite, and it was necessary to adopt anti-mosquito measures 248 such as insecticide treated materials in the outdoor.

We also found that the density of human population was closely associated with dengue transmission. In general, it is believed that the high population density is a risk factor for

251 dengue transmission [6·24]. But in our study, those sharing a crowded household with 2 252 persons and 3 persons and above were less likely to have a dengue infection. The conclusion, 253 however, was contrary to Velascosalas ZI, et al.'s research [25]. The explanation could be that 254 most of one room with 3 persons and above were shared by the parents and their young children which was related to Chinese way to raise kids. When the parents with their kids 255 256 lived in one room, they would pay more attention on using anti-mosquito measures and 257 maintaining a good sanitary environment to avoid the kids being bitten. Secondly, in our 258 related study, the result showed that the married group had a lower rate of infection than the 259 widowed group and the divorced group [20], it also suggested that the married group who 260 usually living in one room with 2 persons and above had a less risk to be infected by dengue 261 virus. Thirdly, when the number of mosquitoes was fixed, the more persons in one room, the 262 lower probability of a person being bitten by the mosquito. Therefore, further research is 263 needed to determine whether more than one person per room is a protective factor or a risk factor for dengue virus infection. 264

According to Shen et al. [26] and Wu PC et al.'s [27] researches, the yearly average temperature higher than 18°C would increase the risk of dengue virus infection. Meanwhile, our study indicated that using air-condition was a protective factor against dengue infection. This reason might be that using air-condition to cool indoor environment can reduce the risk of dengue transmission. Secondly, when using air-condition, doors and windows were commonly shut down, which reduce the chance of mosquitoes entering the room.

Besides, our study showed that the poor quality of indoor daylight increased a 2.27-fold risk for dengue virus infection. The explanation for this is possibly that adult Aedes albopictus prefer to inhabit in weak-light places rather than in those areas with plenty of light [28:29]. So the environment of poor daylight was suitable for the survival of mosquitoes, which lead to the high density of mosquitoes in the room.

Our result failed to find the protective effect of mosquito bed nets on reducing the risk of dengue fever infection. And the result was consistent with Tsuzuki A et al. [30] and Loroñopino MA et al.'s [31] studies. One reason might be that these mosquito bed nets were usually used at night. However, the mosquito of Aedes albopictus was found biting throughout daylight hours, especially in the early morning and late afternoon [32]. Another

explanation could be that the majority of residents including the case group and the control group chose to use mosquito bed nets to prevent mosquito bites, which might lead to lose statistical significance between using mosquito bed net and dengue infection. The third cause might be that good living environment, for instance, the popularity of air-condition and mosquito killing facilities, reduced the demand for mosquito bed nets. Despite the limitation, based on our local experience and some studies' results [33·34], bed nets are still recommended to use not only at night but also during the day [22].

288 Andersson N et al. [35] and Roberto TC et al.'s [12] studies revealed that the 289 government's vector controlling capacity had a very important impact on dengue transmission. Because of the high incidence of dengue fever in Guangdong province in recent years, the 290 291 community neighborhood committees and property management departments organized many 292 health remediation activities under the supervision of the relevant health agent or the Centers for Disease Control and Prevention (CDC) [36], greatly improved the residential living 293 294 environment, reducing mosquito breeding, which may be an explanation of that the variables 295 of domestic sewage disposal, garbage management and residential surroundings were not 296 statistically significant in this study. However, 67.51% of the infections and 60.39% of the controls didn't participate in the community hygiene management intervention activities in 297 298 neighborhood committees or property management organizations in this study. Regardless of 299 the case group or the control group, their public health consciousness need to be strengthened. 300 If the government has a good macro-control system without the support of the masses, it will 301 be unable to fight against disease and establish a sound prevention system.

302

# 303 Limitations:

There are several flaws in this study that should be overcame in the future study. First, cases and controls were identified according to the result of antibody detection. However, the IgG-positive samples might be infected a few years ago, which led to the results of their completed questionnaires were incompatible with the situations when they were infected. Besides, the existence of recall biases which was caused by the inaccuracy of memory could also reduce the authenticity of the questionnaire. Second, in an initial infection, the titers of the IgG antibody was so low after having a fever that the antibody couldn't be detectable [37],

thus the newly infected persons was misdiagnosed as the members of the control group. As a result, the misclassification bias was brought. To reduce these bias, some of the questionnaires were completed by the community doctors, and some of the questionnaires were completed by face-to-face interviews. Third, the data was obtained from serum sample of residents in Guangdong Province from 2013 to 2015 without other extrapolated studies, the model's general practical application is difficult to evaluate at present.

The focus of our study is on residents in communities with mild or asymptomatic dengue virus infection, rather than patients with severe clinical symptoms, which is more representative to explore the risk factors for dengue virus infection in Guangdong province. Besides, this study shows the relationship between dengue infection and individual risk factors, which was beneficial for avoiding being infected by dengue virus. Meanwhile, the results of this study provided clue and basis for dengue fever prevention and control.

323

# 324 Conclusion:

325 The case-control study revealed some risk factors for dengue virus infection to provide 326 guidance for the concrete preventive measures. After analyzing the 28 relevant variables, it 327 is easy to find that when having the behaviors of activities in the park and outdoor sports, it 328 is useful to use mosquito control measures and reduce the exposed area of skin to low down 329 the risk of dengue infection. Moreover, improving the quality of indoor lighting and using 330 air-condition can get the same effect. In the long run, more variables need to be introduced 331 into the logistic regression model and further research should be conducted to provide 332 theoretical basis for formulating prevention and control measures of dengue fever.

333

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- 340 subjects.
- 341
- 342 Supporting information
- 343 S1 Dataset. Complete data.
- 344 S1 Checklist. Strobe checklist case control.
- 345

# 346 **References:**

- Gubler DJ, Meltzer M. Impact of dengue/dengue hemorrhagic fever on the developing world.
   Advances in Virus Research. 1999;53(53):35-70
- 349 2. http://www.who.int/tdr/publications/publications/dengue.
- 350 3. Wen J, Liang F. An etiological and serological study on Dengue epidemic in Guangdong Province.
   351 Chinese Journal of Experimental & Clinical Virology. 1998;12(2):165-168
- 4. Liu C, Liu Q, Lin H, Xin B, Nie J. Spatial analysis of dengue fever in Guangdong Province, China,
  2001-2006. Asia-Pacific journal of public health / Asia-Pacific Academic Consortium for Public
  Health. 2014;26(1):58
- 5. Zhang Y, Wang T, Liu K, Xia Y, Lu Y, Jing Q, et al. Developing a Time Series Predictive Model for
   Dengue in Zhongshan, China Based on Weather and Guangzhou Dengue Surveillance Data. PLoS
   Neglected Tropical Diseases. 2016;10(2):e0004473
- Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic
   problem in the 21st century. Trends in Microbiology. 2002;10(2):100-103
- 7. Thein TL, Leo YS, Fisher DA, Low JG, Oh HML, Gan VC, et al. Risk Factors for Fatality among
  Confirmed Adult Dengue Inpatients in Singapore: A Matched Case-Control Study. PLoS One.
  2013;8(11):e81060
- 8. Pang J, Thein TL, Leo YS, Lye DC. Early clinical and laboratory risk factors of intensive care unit
  requirement during 2004 2008 dengue epidemics in Singapore: a matched case control study.
  Bmc Infectious Diseases. 2014;14(1):649
- 366 9. Moraes GH, De FDE, Duarte EC. Determinants of mortality from severe dengue in Brazil: a
  367 population-based case-control study. American Journal of Tropical Medicine & Hygiene.
  368 2013;88(4):670-676
- 369 10. Branco MR, Luna EJ, Braga Júnior LL, Oliveira RV, Rios LT, Silva MS, et al. Risk factors
  370 associated with death in Brazilian children with severe dengue: a case-control study. Clinics.
  371 2014;69(1):55-60
- 11. Rosenbaum J, Nathan MB, Ragoonanansingh R, Rawlins S, Gayle C, Chadee DD, et al.
  Community participation in dengue prevention and control: a survey of knowledge, attitudes, and
  practice in Trinidad and Tobago. American Journal of Tropical Medicine & Hygiene.
  1995;53(2):111
- 376 12. Roberto TC, Jorge MG, Pierre BZ. Community participation in the prevention and control of

dengue: thepatio limpiostrategy in Mexico. Paediatrics & International Child Health.
2012;32(s1):10-13

- Benthem BHBV, Khantikul N, Panart K, Kessels PJ, Somboon P, Oskam L. Knowledge and use of
   prevention measures related to dengue in northern Thailand. Tropical Medicine & International
   Health. 2010;7(11):993-1000
- 14. Phuanukoonnon S, Mueller I, Bryan JH. Effectiveness of dengue control practices in household
   water containers in Northeast Thailand. Tropical Medicine & International Health.
   2010;10(8):755-763
- 15. Luo L, Liang HY, Hu YS, Liu WJ, Wang YL, Jing QL, et al. Epidemiological, virological, and
   entomological characteristics of dengue from 1978 to 2009 in Guangzhou, China. Journal of Vector
   Ecology. 2012;37(1):230-240
- 16. Gu H, Leung KK, Jing Q, Zhang W, Yang Z, Lu J, et al. Meteorological Factors for Dengue Fever
  Control and Prevention in South China. International Journal of Environmental Research & Public
  Health. 2016;13(9):867
- 17. Fan JC, Lin HL, Hai Xia WU, Wang J, Yang SR, Liu QY. Spatial and temporal distribution
   characteristics of dengue fever in Guangdong province, China during 2006-2011. Chinese Journal
   of Vector Biology & Control. 2013;24(5):389-391
- Wang T, Wang M, Shu B, Chen XQ, Luo L, Wang JY, et al. Evaluation of Inapparent Dengue
   Infections During an Outbreak in Southern China. PLoS Neglected Tropical Diseases. 2015;9(3)
- 396 19. Zhang JH, Yuan J, Wang T. Direct cost of dengue hospitalization in Zhongshan, China:
   397 Associations with demographics, virus types and hospital accreditation. PLoS Neglected Tropical
   398 Diseases. 2017;11(8):e0005784
- 20. Liu JD DYJQ. Dengue Infection Spectrum in Guangzhou: A Cross-Sectional Seroepidemiology
  Study among Community Residents between 2013 and 2015. International Journal of
  Environmental Research and Public Health. 2018;
- 402 21. Liu J, Huang JH, Xiao XL, Dan-Dan YU, Xiang YF, Lai QY, et al. Analysis on the monitoring
  403 results of Aedes albopictus density in Yuexiu District. Chinese Journal of Hygienic Insecticides &
  404 Equipments. 2017;
- 405 22. Kenneson A, Beltránayala E, Borborcordova MJ, Polhemus ME, Ryan SJ, Endy TP, et al.
  406 Social-ecological factors and preventive actions decrease the risk of dengue infection at the
  407 household-level: Results from a prospective dengue surveillance study in Machala, Ecuador. Plos
  408 Negl Trop Dis. 2017;
- 409 23. Rezza G. Aedes albopictus and the reemergence of Dengue. Bmc Public Health. 2012;12(1):1-3
- 410 24. Jing QL, Yi-Lan LI, Chen ZQ, Xiao Y, Cao Q, Jia-Hai LU, et al. Spatial pattern and driving factors
  411 of dengue virus-4 epidemics in Guangzhou. Journal of Tropical Medicine. 2016;
- 412 25. Velascosalas ZI, Sierra GM, Guzmán DM, Zambrano J, Vivas D, Comach G, et al. Dengue
  413 Seroprevalence and Risk Factors for Past and Recent Viral Transmission in Venezuela: A
  414 Comprehensive Community-Based Study. American Journal of Tropical Medicine & Hygiene.
  415 2014;91(5):1039-48
- 416 26. SHEN, Chuan, JING, Long, Chun, Quan, et al. The Impacts of Mosquito Density and
  417 Meteorological Factors on Dengue Fever Epidemics in Guangzhou, China, 2006-2014: a
  418 Time-series Analysis. Biomedical and Environmental Sciences. 2015;28(5):321-329
- 419 27. Wu PC, Lay JG, Guo HR, Lin CY, Lung SC, Su HJ. Higher temperature and urbanization affect the
   420 spatial patterns of dengue fever transmission in subtropical Taiwan. Science of the Total

- 421 Environment. 2009;407(7):2224-2233
- 422 28. Gong DF, Zhou HN. Progress in Dengue fever important vector Aedes albopictus in China. Chinese
  423 Journal of Vector Biology & Control. 2009;20(6):607-610
- 424 29. Crepeau TN, Healy SP, Kristen BH, Isik U, Ary F, Fonseca DM. Effects of Biogents Sentinel Trap
  425 Field Placement on Capture Rates of Adult Asian Tiger Mosquitoes, Aedes albopictus. PLoS One.
  426 2013;8(3):e60524
- 30. Tsuzuki A, Thiem VD, Suzuki M, Yanai H, Matsubayashi T, Yoshida LM, et al. Can Daytime Use
  of Bed Nets Not Treated with Insecticide Reduce the Risk of Dengue Hemorrhagic Fever Among
  Children in Vietnam? American Journal of Tropical Medicine & Hygiene. 2010;82(6):1157
- 430 31. Loroñopino MA, Machainwilliams C, Gomezcarro S, Nuñezayala G, Losoya A, Aguilar L, et al.
  431 Towards a Casa Segura: A Consumer Product Study of the Effect of Insecticide-Treated Curtains on
  432 Aedes aegypti and Dengue Virus Infections in the Home. American Journal of Tropical Medicine &
  433 Hygiene. 2013;89(2):385
- 434 32. Trpis M, Mcclelland GA, Gillett JD, Teesdale C, Rao TR. Diel periodicity in the landing of Aedes
  435 aegypti on man. Bulletin of the World Health Organization. 1973;48(5):623-9
- 436 33. Vanwambeke SO, van Benthem BH, Khantikul N, Burghoorn-Maas C, Panart K, Oskam L, et al.
  437 Multi-level analyses of spatial and temporal determinants for dengue infection. International
  438 Journal of Health Geographics. 2006;5(1):5
- 439 34. Lenhart A, Orelus N, Maskill R, Alexander N, Streit T, Mccall PJ. Insecticide-treated bednets to
  440 control dengue vectors: preliminary evidence from a controlled trial in Haiti. Tropical Medicine &
  441 International Health. 2008;13(1):56-67
- 442 35. Andersson N, Navaaguilera E, Arosteguí J, Moralesperez A, Suazolaguna H, Legorretasoberanis J,
  443 et al. Evidence based community mobilization for dengue prevention in Nicaragua and Mexico
  444 (Camino Verde, the Green Way): cluster randomized controlled trial. 2015;351:h3267
- 36. Pan HF, Xiao-Xian YE, Chen CJ, Zhao JY, Lin ZY. Study on prevention and control of Dengue
  from perspective of public health. Chinese Journal of Public Health Management. 2015;
- 447 37. Guzman MG, Harris E. Dengue. Lancet. 2015;385(9966):453-465
- 448