Association between the occurrence of albuminuria and the risk of early dementia among older people upon health examination: a community-based cohort study in Taiwan

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ABSTRACT

Objectives This study aimed to investigate the associations between biochemical markers, renal function, health behaviours and dementia among older people.

Design A retrospective cohort study.

Setting Community-based health examination database from Taipei city.

Participants In total, 35 434 older people were included from February 2005 to December 2012. To assess changes in renal function, we selected participants who attended health examinations at least twice and responded to the AD8 questionnaire in 2012. We excluded those with dementia at baseline.

Primary outcome measures Early dementia was assessed using the AD8 questionnaire in 2012. Explanatory variables included demographic factors, health behaviours, biochemical markers and renal function. We used a Cox proportional hazard model to estimate the HR for early dementia onset.

Results Individuals with mild albuminuria (HR 1.228; 95% CI 1.066 to 1.414), lower eGFR (HR 1.549; 95% CI 1.319 to 1.820) and higher age (HR 1.022; 95% CI 1.015 to 1.028) were associated with a high risk of early dementia. Older people with no alcohol intake (HR 0.872; 95% CI 0.794 to 0.958), and higher education levels (HR 0.647; 95% CI 0.589 to 0.710) were at a low risk of early dementia.

Conclusions Elevated mild albuminuria and low eGFR were associated with a high risk of early dementia in this community-based cohort. Routine health examinations for older people can help screen out the high-risk population, and clinical management might reduce or delay the risk of early dementia.

INTRODUCTION

Dementia is characterised by a decline in memory or cognitive functions, thus affecting mental abilities and daily activities. Dementia is not an aspect of normal ageing, and it could significantly affect countries with substantial population ageing. Over 9.9 million new dementia cases emerge worldwide annually, with an average of one case every 3.2 s. In 2015, approximately 47 million individuals had dementia, and this number was predicted to triple by 2050. In Asia, a meta-analysis reported that the number of individuals with dementia is approaching 8.4 million in China, Hong Kong and Taiwan. Comprehensive health insurance in Taiwan facilitates robust estimation of dementia prevalence. A nationwide survey from 2011 to 2013 in Taiwan estimated that the age-adjusted dementia prevalence was 8.04% (0.13 million) among individuals aged ≥65 years. This prevalence rate in Taiwan is expected to double every 20 years; the number of individuals with dementia will approach 0.32 million by 2030 and exceed 0.6 million by 2050.

Dementia patients need long-term health and social care owing to various disabilities, including financial and social burdens on both the healthcare system and society. The total expenditure for dementia management worldwide was US$422 billion in 2009. In Taiwan, the cost increases with the severity...
of the disease, with mild dementia costing US$7288 per year and severe dementia costing US$14 655 per year. A continuous tendency to incur such expenses can be expected with an increase in the dementia population. Therefore, dementia has emerged as a significant global challenge in both health and social care in the 21st century.

Previous studies have investigated the cause of dementia to provide better care and for prevention. Alzheimer disease is the most common cause, contributing to 60%–80% of dementia cases. Another aetiology is vascular dementia, which can occur after a stroke or vascular disease. Symptoms of vascular disease can be observed in chronic kidney disease (CKD) because blood pressure and water content are not regulated during kidney dysfunction, thus increasing the cardiac output (owing to poor drainage). Similarly, low cardiac contractility reduces blood perfusion and renal function, resulting in vascular dementia owing to repeated vascular insults caused by CKD. One US study reported that most domains of cognitive function seem to be affected by poor renal function in all stages of CKD due to renal function being damaged by microvascular disorders. However, a longitudinal study on new-onset dementia considered renal function but reported no strong association of kidney disease severity and progression with incident dementia. A previous study among the elderly in China showed that the relative risk of developing cognitive decline was 4.03 among participants with low estimated glomerular filtration rate (eGFR) (30–59 mL/min/1.73 m²) compared with participants with high eGFR (≥60 mL/min/1.73 m²). Early stage of kidney disease was correlated with cognitive decline. A study in Japan with subjects aged ≥60 years indicated albuminuria was a risk factor for the development of dementia (both Alzheimer’s disease and vascular dementia). Furthermore, albuminuria and low eGFR level were associated with higher risk of vascular dementia. These studies revealed that kidney function could be correlated with cognitive function in the elderly. Renal function tests can be conveniently performed during routine health examinations, and this is a suitable screening tool for early diagnosis of dementia.

Dementia is a major problem among the elderly. CKD is common among older individuals, and kidney function may also decrease with age. We believe that kidney function is a good monitoring indicator of early dementia. Controlling and maintaining kidney function could reduce the risk of dementia and help prevent it through routine health examination. Because previous studies have rarely used data from health examination of older individuals to examine the association between renal function and the early onset of dementia, this study aimed to investigate whether renal function, biochemical markers, and health behaviours are associated with early dementia.

METHOD

Study design and ethical statement

This retrospective longitudinal cohort study was based on data obtained from a health examination database of older people. Participants were enrolled and provided written informed consent and to the Taipei City Government to record health examination data for research purposes. Data were curated in the Taipei Geriatric Health Examination Database, and labels were deidentified before release.

Approximately 45 000 maximised theoretical capacity of participants registered for this geriatric health examination annually from February 2005 to December 2012. Their participation was voluntary. The AD8 questionnaire was first introduced and used in 2012. Thus, we first selected 40 021 older people in 2012 from among 34 8067 older people from 2005 to 2012 who were undergoing health examination in Taipei City. The endpoint of this study was 2012. Simultaneously, AD8 scores and the results of health examinations were recorded. The remaining baseline risk factors were computed from 2005 to 2012. Although there were 34 8067 older people from 2005 to 2012 participating in the health examination, we had to select participants who also had health examinations in 2012. Thus, there were 40 021 older people included in the first wave of selection. Since our purpose is to evaluate the change from being dementia free to early dementia in these observed years, we excluded individuals with dementia at baseline (n=126), those with no AD8 scores in 2012 (n=437), and those who took the health examination only once (n=3587). Finally, 35 434 subjects were enrolled for further assessment (figure 1). Among the original 40 021 people, only 8.96% (3587/40 021) had only one health visit before. The frequency distribution of number of visits in our study population is shown in online supplemental figure 1.

Cohort description

This community-based cohort study used data from the Taipei City Elderly Health Examination Database. The study period was February 2005 to December 2012. The Taipei City government provides free annual health examinations for older people in Taipei City. A two-stage approach was used to recruit the participants.
In the first stage, aboriginals, those living alone, those living in low-income households, and disabled individuals were recruited through telephone and internet registration at the end of February each year during the study period. In the second stage, all older people registered in Taipei City, who could register for the examination through the telephone, internet or on-site registration in the first week of March each year were recruited. All participants received a health examination once annually. To observe changes in renal function, we only selected participants with at least two visits in this study.

Health examination included a standardised medical examination and a questionnaire addressing several health-related topics. The examination included health history, physical assessment (ie, weight, height, blood pressure, pulse and waist circumference), depression screening, early dementia screening (AD8), biochemistry examination, routine urine examination (urine collected on site), routine blood examination, oral examination and stool examination. The health questionnaire was self-reported, with the prompt assistance of the medical staff if the participants were unable to provide responses. This study used the Mandarin version of the AD8 questionnaire, an early dementia screening scale, in 2012 as the outcome. Variables included demographic factors and health-related behaviours, such as milk intake, vegetable intake, smoking and alcohol consumption. Furthermore, values of biochemical examination including blood sugar before meals (AC), albumin, serum globulin (GL) and blood urea nitrogen (BUN) were considered.

Patient and public involvement
This study obtained secondhand data; participants did not receive feedback on the results and were not involved in the study.

AD8 questionnaire
The health examination data included the AD8 questionnaire—an eight-item questionnaire assessing early dementia. The AD8 questionnaire included yes-or-no questions, and two or more answers of yes were strongly suggestive of dementia. A previous validation study of the AD8 questionnaire conducted among Taiwanese individuals revealed a sensitivity of 97.6% and a specificity of 78.1%. The questionnaire includes memory, orientation, executive functioning, and interest in activities. Furthermore, the questionnaire items included difficulties in judgement, reduced interest in activities and hobbies, repeating the same problem or story statement, difficulties in learning to use tools and equipment, forgetting the year and month, finding it challenging to deal with complicated finances, and failing to remember appointment times. Eight questions were listed to investigate continuous thinking and memory issues.

Demographic variables, health behaviours and biochemical data
We used a self-reported questionnaire including demographic characteristics, health behaviours, and biochemical results. Demographic characteristics such as age, sex, body mass index (BMI) (classified into four levels: BMI <18.5 kg/m², 18.5 ≤BMI <24 kg/m², 24 ≤BMI <27 kg/m² and BMI ≥27 kg/m²), educational level (categorised into three levels: university and above, senior and junior high school, and primary level and below) were collected. Health behaviours including long-term medication use (yes or no), exercise (yes or no) and substance usage (alcohol drinker or non-drinker and smoker or non-smoker) were gathered. Individual health information including long-term medication use and physical and biochemical values (ie, BMI, albuminuria ‘−’, negative,<10 mg/dL; ‘+’, trace, 10–20 mg/dL; ‘+’, 21–30 mg/dL; ‘++’, 31–100 mg/dL; ‘+++’, 101–300 mg/dL; ‘++++’, ≥301 mg/dL), eGFR (mL/min/1.73 m²), BUN (mg/dL), albumin (mg/dL), AC (mg/dL) and globulin (mg/dL)) were obtained. The eGFR was determined as follows18:

\[
186 \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203}
\]

Male × 1; Female × 0.742

Independent variables included continuous variables such as age, BMI, AC, GL and BUN and categorical binary variables (yes or no) including smoking, alcohol consumption, and long-term medication use. Other categorical variables, such as groups of eGFR, albuminuria, education level and sex, were also assessed.

Statistical analyses
To determine the risk factors that were significantly associated with early dementia, survival analysis with a Cox proportional hazard model was performed. The changes over time in the different levels of eGFR or albuminuria levels of early dementia are presented in the survival plot. We adjusted age and gender in the analysis. A Cox proportional hazard model helped evaluate the probability of early dementia in 2012. The starting time was set at the time of the first health examination date. We simultaneously obtained baseline information, and the data were censored in the last health examination for each participant. The average follow-up duration was 5.05 years.

We determined the occurrence of early dementia from the censoring time. All p values were two tailed, and p<0.05 was considered significant. Statistical analyses were performed using SPSS V.25.0 (IBM).

RESULTS
Study population
Tables 1 and 2 display the descriptive statistics of categorical and continuous variables. The AD8 score was divided into two categories (a score of <2 was considered normal, whereas a score of ≥2 was indicative of early dementia) on the basis of previous results. In the Taipei City health
examination data, 88.1% of the older people received scores of <2, whereas 11.9% had scores of ≥2. Most participants were using long-term medication (67.7%), did not consume alcohol (76.1%), were nonsmokers (86.6%), were male (47.7%), had at least a junior high school education level (67.9%), and had normal albuminuria (85.3%).

The outcomes of physical and biochemical examination for the study population are summarised in table 2. All average biochemical values were within normal reference levels, including AC (103.88 mg/dL, SD=23.42), serum albumin (4.37 mg/dL, SD=0.69), GL (3.02 mg/dL, SD=0.86), BUN (16.3 mg/dL, SD=6.01), age (71.07 years, SD=5.63) and BMI (23.97, SD=3.33).

\( \chi^2 \) analysis

A \( \chi^2 \) test was performed separately for each independent variable to assess the associations of an AD8 score of <2 with the personal characteristics in table 3. Albuminuria, eGFR class, education level, sex and alcohol consumption differed significantly between the group with AD8 scores of <2 and the group with AD8 scores of ≥2.

Survival analysis

The risk and protective factors associated with AD8 were further examined through survival analysis (table 4). The survival function at mean of covariates in online supplemental figure 2 showed the probability of survival decreased with the time changes. In online supplemental figure 3, we depicted the cumulative hazard function to evaluate all covariates of their mean values. As shown in online supplemental figure 3, this hazard function peaks over time. Thus, the risk of event occurrence increases over time. The survival curves in the appendix (see online supplemental figures 4–6) show the difference between different groups of albuminuria and different levels of eGFR. The hazard of this study population with different eGFR or albuminuria levels changed with time. Compared with normal albuminuria, individuals with albuminuria + and ++ had a higher HR 1.228, 95% CI 1.066 to 1.414. Higher eGFR was associated with lower HR (eGFR <45 mL/min/1.73 m\(^2\), HR=1.549; eGFR=45–59 mL/min/1.73 m\(^2\), HR=1.244; eGFR=60–74 mL/min/1.73 m\(^2\), HR=1.149; \( p=0.004 \)). Therefore, a high eGFR may be associated with a high risk of early dementia. Regarding education levels, individuals with a senior or junior high degree (HR=0.776, 95% CI 0.715 to 0.842) and those with a university or higher degree (HR=0.647, 95% CI 0.589 to 0.710) had lower HRs than those with an education level of primary school or below. Regarding health behaviour, non-drinkers (HR=0.872, 95% CI 0.794 to 0.958) had a lower HR than drinkers did. Regarding age, older people had a higher HR (HR=1.022, 95% CI 1.015 to 1.028) than younger individuals did.

DISCUSSION

This study of 35434 older people indicated that high albuminuria and low eGFR levels are associated with a high risk of early dementia. This finding is consistent with those of previous studies reporting that albuminuria is associated with worse cognitive function.\(^{19}\)\(^{20}\) Moreover, moderate albuminuria, but not severe albuminuria, was significantly associated with early dementia. Low eGFR was also significantly associated with early dementia. Previous studies investigating the association between eGFR and cognitive function have presented inconsistent results.\(^{21}\)\(^{22}\)

Although some cross-sectional studies have reported that low eGFR is associated with cognitive impairment,\(^{11\,\,23}\)
the results have been inconsistent among older males. Rigorous testing and monitoring of kidney function and a comprehensive evaluation of dementia would be practical solutions in future assessments to better understand this association. The biological mechanisms, in addition to vascular contributions, among albuminuria, eGFR and dementia, require further study.

A previous meta-analysis involving 32 eligible studies reported that albuminuria is independently associated with cognitive impairment, dementia and cognitive decline and that vascular dementia and cognitive performance were primarily affected by microvascular disease. Therefore, microvascular disease mediates the association between poor renal function and dementia. Another meta-analysis reported that albuminuria is associated with a higher risk of cognitive impairment or dementia. However, the association between renal dysfunction and cognitive impairment or dementia was modest. We obtained data from older people aged ≥65 years. These results indicate that high albuminuria and low eGFR are associated with a higher risk of cognitive disorders and early dementia, concurrent with the aforementioned reports. Furthermore, eGFR had a dose–response association with early dementia; the lower the eGFR, the higher the HR.

Table 2  Outcomes of physical and biochemical assessments of the study population

| Outcomes                     | Minimal | Maximum | Mean | Medium | SD   | IQR |
|------------------------------|---------|---------|------|--------|------|-----|
| Glucose                      | 1.06    | 331.00  | 103.88| 98     | 23.42| 17.0|
| Serum albumin                | 0.50    | 47.10   | 4.37 | 4.40   | 0.69 | 0.30|
| Globulin                     | 0.80    | 132.00  | 3.02 | 3.00   | 0.86 | 0.50|
| Blood urea nitrogen          | 0.66    | 224.00  | 17.21| 16.30  | 6.01 | 5.40|
| Age                          | 65.00   | 100.00  | 71.07| 70     | 5.63 | 9.0 |
| BMI                          | 10.58   | 43.28   | 24.13| 23.97  | 3.33 | 4.17|
| serum creatinine             | 0       | 241     | 1    | 0.9    | 1.37 | 0.3 |
| eGFR                         | 0.14    | 1256    | 74.91| NA     | 23.22| 24.6|
| Average follow-up time (days)| 108     | 2766    | 1845 | NA     | 726.73| 1145|

Data are presented as numbers (N).
BMI, body mass index; NA, not available.

Table 3  Characteristics of older individuals with or without early dementia

| Characteristics          | AD8 <2 | AD8≥2 | P value | X² |
|--------------------------|--------|-------|---------|----|
| Albuminuria              |        |       |         |    |
| −, ±                     | 26653  | 94.0  | 3561    | 92.9| 0.02| 7.818|
| +, ++                    | 1599   | 5.5   | 253     | 6.6 |     |      |
| ++++, ++++               | 130    | 0.5   | 19      | 0.5 |     |      |
| Long-term medication     |        |       |         |    |
| No                       | 8189   | 27.9  | 1043    | 27.3| 0.450| 0.570|
| Yes                      | 21193  | 72.1  | 2779    | 72.7|     |      |
| eGFR                     |        |       |         |    |
| >75                      | 14339  | 50.9  | 1802    | 49.3| 0.031| 4.686|
| 60–74                    | 7799   | 27.7  | 1020    | 27.9|     |      |
| 45–59                    | 4667   | 16.6  | 641     | 17.5|     |      |
| <45                      | 1354   | 4.8   | 191     | 5.2 |     |      |
| Smokes or not            |        |       |         |    |
| No                       | 27136  | 93.8  | 3544    | 94.0| 0.66| 0.194|
| Yes                      | 1779   | 6.2   | 225     | 6.0 |     |      |
| Education                |        |       |         |    |
| Primary or less          | 7850   | 26.7  | 1291    | 33.8| <0.0001| 124.358|
| Senior and junior high   | 11287  | 38.4  | 1501    | 39.3|     |      |
| University and above     | 10245  | 34.9  | 1030    | 26.9|     |      |
| Gender                   |        |       |         |    |
| Female                   | 14308  | 48.7  | 1999    | 52.3| <0.0001| 17.596|
| Male                     | 15074  | 51.3  | 1823    | 47.7|     |      |
| Alcohol intake           |        |       |         |    |
| No                       | 23832  | 81.3  | 3147    | 82.4| 0.083| 3.014|
| Yes                      | 5495   | 18.7  | 671     | 17.6|     |      |

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Sex and age were previously considered the most prominent dementia risk factors; female sex is a risk factor for mild cognitive impairment. Our results are partially consistent with previous studies reporting a higher age is significantly associated with early dementia; however, sex was not a significant factor in the present study. Decreased weight and cognitive impairment result in progressive degeneration and may potentially accelerate brain damage, potentially owing to poor nutrition, chronic disease, and lack of physical activity. BMI was not significantly associated with potential early dementia. Furthermore, alcohol consumption was associated with an increased risk of early dementia. One study reported that alcohol consumption of ≤2 units/day could reduce the risk of dementia among older Japanese adults. However, a previous review reported a dose–response effect of alcohol consumption on the deterioration of cognitive function. Frequent heavy alcohol consumption may damage brain function and decrease cognitive functions, whereas light to moderate alcohol consumption has protective effects. This study did not report a dose–response effect because the questionnaire simply provided information regarding whether alcohol consumption had an effect. Podcasy and Epperson emphasised behavioural interventions including diet and exercise for both sexes to achieve beneficial effects. Thus, policy-makers should develop preventative programmes for both sexes.

| Variables             | B     | P     | HR   | 95% CI          |
|-----------------------|-------|-------|------|-----------------|
| eGFR                  |       |       |      |                 |
| 60–74 vs ≥75          | 0.139 | 0.013*| 1.149| 1.030 to 1.282  |
| 45–59 vs ≥75          | 0.219 | 0.004*| 1.244| 1.074 to 1.441  |
| <45 vs ≥75            | 0.438 | <0.001‡| 1.549| 1.319 to 1.820  |
| eGFR                  |       |       |      |                 |
| Continuous            | −0.002| 0.004† | 0.998| 0.996 to 0.999  |
| Albuminuria           |       |       |      |                 |
| +, ++ vs −, ±         | 0.205 | 0.004*| 1.228| 1.066 to 1.414  |
| ++++, ++++ vs −, ±    | 0.069 | 0.796 | 1.072| 1.072 to 0.634  |
| Alcohol intake        |       |       |      |                 |
| No versus yes         | −0.137| 0.004*| 0.872| 0.794 to 0.958  |
| Long-term medication  |       |       |      |                 |
| No versus yes         | −0.065| 0.097 | 0.937| 0.867 to 1.012  |
| Smoking               |       |       |      |                 |
| No versus yes         | 0.095 | 0.203 | 1.100| 0.950 to 1.274  |
| Gender                |       |       |      |                 |
| Male versus female    | −0.009| 0.890 | 0.991| 0.866 to 1.133  |
| Education             |       |       |      |                 |
| Senior and junior high versus primary and less | −0.254| <0.001‡| 0.776| 0.715 to 0.842  |
| University and above versus primary and less | −0.436| <0.001‡| 0.647| 0.589 to 0.710  |
| BMI                   |       |       |      |                 |
| 18.5≤BMI<24 vs BMI <18.5 | 0.112 | 0.233 | 1.119| 0.931 to 1.344  |
| 24≤BMI<27 vs BMI <18.5 | 0.055 | 0.570 | 1.056| 0.875 to 1.275  |
| BMI≥27 vs BMI <18.5   | 0.019 | 0.849 | 1.019| 0.837 to 1.275  |
| Age                   | 0.021 | <0.001‡| 1.022| 1.015 to 1.028  |
| GL                    | −0.002| 0.939 | 0.998| 0.954 to 1.044  |
| AC                    | −0.001| 0.272 | 0.999| 0.998 to 1.001  |
| BUN                   | 0.002 | 0.479 | 1.002| 0.998 to 1.008  |
| Alb                   | 0.003 | 0.905 | 1.003| 0.960 to 1.047  |

*p<0.05. †p<0.01. ‡p<0.001.
AC, blood sugar before meals; Alb, albumin; BMI, body mass index; BUN, blood urea nitrogen; GL, serum globulin.

Table 4. Risk factors for early dementia.
Moreover, we excluded those with self-reported dementia. In cut-off value of AD8 set at two can discriminate between clinical dementia rating scale (r=0.834, p<0.0001). The high sensitivity (97.6%) to detect early dementia, and was more representative than those of previous studies.39 rather than hospitalised patients; thus, the population comprised older individuals from the community examined at least twice. Furthermore, this study population was able to distinguish them from our data. In addition, our study did not collect physical and neurological examinations, interviews of the families and attending physicians or medical records to diagnose dementia. Further clinical diagnosis would help to screen individuals with cognitive impairment and improve estimation. In addition, we did not distinguish between Alzheimer disease and vascular dementia. Based on a previous study by Yang et al,12 the AD8 questionnaire is a good tool with high sensitivity (97.6%) to detect early dementia, and it was highly correlated with the sum of the boxes of an clinical dementia rating scale (r=0.834, p<0.0001). The cut-off value of AD8 set at two can discriminate between normal participants and those with mild dementia. In order to increase accuracy, clinical diagnosis is needed. Moreover, we excluded those with self-reported dementia at the beginning. However, those who were not excluded may also have had dementia but been unaware of it. Finally, the underestimation of health behaviours from self-reported questionnaires could have been affected by the socially desirable expectations. However, no further objective data were available to verify the accuracy of the self-reported health behaviours.

Nonetheless, this study had several strengths. The present cohort comprised older individuals in Taipei, Taiwan, who had undergone a comprehensive health examination at least twice. Furthermore, this study population comprised older individuals from the community rather than hospitalised patients; thus, the population was more representative than those of previous studies.39 This community database provides fruitful information regarding early dementia and potential prevention strategies.

In conclusion, among the older individuals in the present study, elevated mild albuminuria, low eGFR and alcohol consumption were associated with early dementia. Advocating community health examinations would help identify groups with a high risk of early dementia.

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Acknowledgements We thank the Department of Health, Taipei City Government for allowing the use of data for this research and all of participants.

Contributors T-JT, Y-TY and Y-HY reviewed the literature and made substantial contributions to the conception and design. T-JT and Y-TY refined the data and performed statistical analysis. Y-HY and Y-HC interpreted the results. Y-HY and T-CC conceptualised and designed the paper, interpreted the results and drafted the manuscript. All authors have read and approved the final manuscript.

Funding This research was supported by a grant from the Ministry of Science and Technology, Taiwan (MOST-106–2627-M-001-003) and a grant titled ‘Multidisciplinary Health Cloud Research Program: Technology Development and Application of Big Health Data’ from Academia Sinica.

Disclaimer The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Review Board (IRB) on Biomedical Science Research, Academia Sinica (AS-IRB02-104182).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The raw data are confidential and cannot be readily shared. Researchers must obtain permission from the IRB and apply for access to the data from the Department of Health, Taipei City Government.

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