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短期臭氧暴露與全死因、糖尿病、心血管疾病死亡之關係

Association of Short-term Ozone Exposure with Total, Diabetes, and Cardiovascular Diseases Mortalities

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進入職衛所兩年的時光，經歷了許多挫折與成長。在這段時間中，最感激的莫過於指導老師鄭尊仁教授，在我每一個犯錯的過程中耐心的給予我教育與引導，讓我在學術領域蹣跚學步的過程中有了長足的進步，並讓我在學術的殿堂外也了解其他做人做事的道理。謝謝鄭老師給予我每一次犯錯與改過的空間，也滿心感激鄭老師不吝花費時間給我各方面的建議與指導。

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吳亭亭

謹致　99.7

摘要

在流行病學研究上已有文獻指出臭氧暴露與呼吸道及心血管疾病死亡具有相關性，然而在臭氧暴露與糖尿病死亡的關係上，尚未有一致的研究結果。本研究目的為探討大氣臭氧暴露對全死因、心血管疾病與糖尿病死亡之危險性。

本研究使用 2006 至 2008 年衛生署死亡資料庫，選取戶籍位於大台北地區(全台北市與部分台北縣鄉鎮市)死亡年齡高於五十歲之糖尿病死亡(ICD9, 250)個案(共 5,767 個案數)為研究對象，分析糖尿病死亡與臭氧暴露之危險性。全死因與心血管疾病死亡個案(ICD9, 390- 459)根據糖尿病死亡個案之年齡與性別分別以 1:2 之比例亂數選出(各 11,543 個案數)，分析大氣臭氧暴露對全死因與心血管疾病死亡之危險性，進一步比較臭氧暴露對不同的疾病死亡風險。環境資料使用臺灣環保署環境監測站空氣品質監測網提供之量測數據，利用大台北地區之 15 個監測站之日平均量測值為死亡個案之暴露濃度。除了日平均值的計算，臭氧最大八小時值亦納入分析。在暴露評估模式上，以 1 天至 7 天的臭氧濃度移動平均值，以及 1 天至 7 天的單日延遲臭氧濃度代表不同的累積暴露情形。在此研究中，使用病例交叉研究設計，以死亡為健康效應，並定義危害期於死亡當天至前六天(共七個危害期)，對照期為危害期前一、二、三、四週相對應之日期做選擇，分析大氣臭氧暴露對死亡造成之風險。在統計模式中，控制溫度、濕度、懸浮微粒($PM_{2.5}$與PM_{10})等影響因子。

本研究發現糖尿病在臭氧暴露下有顯著死亡風險，以 24 小時臭氧移動平均值模式並控制溫度、濕度、$PM_{2.5}$(或PM_{10})等影響因子下，臭氧暴露對全死因、心血管疾病死亡與糖尿病死亡有累積效應情況。男性與性別 50- 65 歲糖尿病個案有顯著

死亡風險。在利用最大八小時臭氧濃度值做分析時，亦發現有相似的結果。與全死因及心血管死亡相比，暴露於大氣臭氧下，糖尿病沒有較高的死亡風險。因本研究使用死亡資料庫提供之原死因為個案篩選條件，故糖尿病死亡個案確切死因在未來研究中應該要再釐清以利分析。

Abstract

Background: Associations between ozone exposure and mortality have been reported, particularly in respiratory and cardiovascular diseases (CVD). However, the relationship between ozone (O_3) exposure and diabetes mellitus (DM) mortality remains unclear.

Objective: To compare the relationships between ozone exposure with total mortality and those caused by CVD and DM.

Method: DM deaths (International ICD-9, 250; N=5,767) more than 50 years of age from National Mortality Registry in metropolitan Taipei, Taiwan between 2006 and 2008 were included for analysis. For comparison, total death and CVD deaths (ICD-9, 390- 459, N=11534) were chosen by match with gender and age with DM deaths. Average levels of ozone each day were calculated from 15 monitoring stations of Taiwan EPA in this area; daily maximum 8-hour concentrations of ozone were computed as well. Case-crossover design was applied to examine the risk between the hazard and reference periods while daily moving average from 0-day (the day of death) to 7-day was used and 4 reference days were chosen by every 7 days before the day of death for 1 month. Temperature and relative humidity were included in the single pollutant model, and PM_{10} or $PM_{2.5}$ was further adjusted in two-pollutant model.

Results: In two-pollutant model with $PM_{2.5}$ adjusted, the trend of accumulative effect of ozone was observed in total death, CVD and DM deaths. Diabetics (OR=1.11, 1.03-1.19) , total death (OR), and CVD (OR=1.10, 1.04-1.16) were at risk for deaths in an interquartile range increase of ozone (11.6 ppb) within 7 days exposure. Similar results were also obtained with maximum 8-hour ozone exposure. However, the risk of diabetes deaths from ozone exposure was not higher than those of total deaths and CVD deaths. In this study, either PM_{10} or $PM_{2.5}$ was not associated with ozone exposure.

Conclusion: Increased ozone exposure is associated with mortality in total deaths, DM and CVD deaths. However, diabetics were not at higher risk with exposure to ozone. Because the underlying causes of death from diabetes are not available from the National Mortality Registry, specific causes of death from diabetes need to be specified in the future study.

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Chapter 1 Background and Objective

Air pollution exposure is associated with cardiopulmonary mortality (1; 2) and morbidity (3; 4). Recently, the effect of particle exposure on health has become a concern for the general public and susceptible populations. The association between particle exposure and mortality in general and from cardiovascular diseases (CVD) has been established (5-7) . However, the health effect of ozone (O_3) exposure remains unclear.

O_3 exposure is associated with total (8) and respiratory mortality (9). Epidemiology studies have shown that O_3 exposure is associated with hospital admission and emergency visits for respiratory diseases (10; 11). The association between O_3 exposure and CVD remains unclear. Several studies have reported that increased O_3 levels may be associated with CVD mortality and morbidity (8; 12). However, other studies did not obtain the same findings (3; 4).

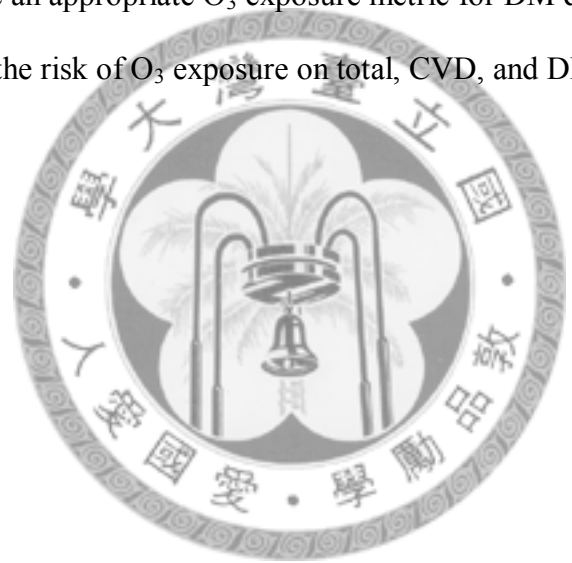
Previous studies have shown that the associations between air pollutants and cardiopulmonary diseases are prominent in susceptible groups such as the elderly (13), asthmatics (14), and those with cardiopulmonary diseases (15) or the diabetics (16-18). Ambient particles have a greater effect on the mortality (18; 19) and number of daily hospital admissions of diabetics (18). Diabetes mellitus (DM) is a chronic disease accounting for more than 3 million deaths in the world each year according to World Health Organization (20). It has become one of the top ten leading causes of death in many countries around the world (21; 22). However, the increased susceptibility to O_3 exposure is unclear (13).

Different exposure metrics for O_3 exposure have been used in epidemiological studies with inconsistent results (8; 12; 13; 23). In this study, we used the maximum

8-hour mean and the daily average combined with either single-lag or moving average models to determine associations between O_3 exposure and total mortalities and those caused by CVD or DM.

The associations of DM deaths and O_3 exposure are less consistent (Table. 1 and Table. 2) with different O_3 exposure metrics and models. In the present study, we applied case-crossover study design to explore the risk of O_3 exposure and DM deaths, and our aims are as following:

1. To explore the association between O_3 exposure and DM mortality;
2. To determine an appropriate O_3 exposure metric for DM deaths;
3. To compare the risk of O_3 exposure on total, CVD, and DM mortalities.



Chapter 2 Literature review

2.1 Air pollution and health

2.1.1 PM exposure and Health

Air pollution exposure has been associated with cardiopulmonary mortality and morbidity. The association between cardiovascular disease and air pollutants including particulate matter (PM) and O_3 was reported in epidemiology studies (1) and a plausible mechanism of PM exposure with CVD was conducted. In one review article, the author pointed out that both short-term and long-term air pollutants exposure were associated with an increase of death from cardiopulmonary diseases (2). Schwartz et al. conducted a epidemiology research to explore the association between air pollutants and emergency admissions from pneumonia and myocardial infarction (3), and they found emergency admissions were significantly associated with increased air pollutants. A multi-city study illustrated that air pollutants including carbon monoxide (CO), nitrogen dioxide (NO_2), O_3 and PM were associated with cardiopulmonary emergency visits (10). Peel et al. investigated potentially sensitive groups from emergency visits among CVD patients, and they found that CVD patients diagnosed with diabetes were at risk of air pollutants exposure on CVD morbidity (4).

Recently, health effect of particle exposure has been a concern for general public and susceptible populations. The associations between particle exposure and mortality from total and cardiovascular diseases have been reported in many studies. Daily total mortality was associated by 0.6% with per 10-μg/m^3 fine particles (particulate matter which aerodynamic diameter less than 2.5 μm, $PM_{2.5}$) (5). Another study found that there was 0.98% increase in total mortality for per 10 μg/m^3 $PM_{2.5}$ increase, and the association between $PM_{2.5}$ exposure and other specific causes of death including CVD,

myocardial infarction, and respiratory diseases were found that the higher air pollutant concentration levels the higher the mortality (7). With different lag days of O_3 exposure, consistent results were observed in these studies that PM was associated with hospital admission for respiratory diseases (24) and CVD (3).

2.1.2 O_3 exposure and health

In Taiwan, Pollutant Standards Index (PSI) is used to indicate the pollutant level of the day, and the value of 100 is defined as the maximum permitted concentrations of pollutants. From 2006 to 2009, PM_{10} and O_3 were the main sources of pollutants exceeded the permitted concentration (25) in Taiwan, and the percentages of days with PSI> 100 of O_3 were higher than 60%.

The importance of O_3 exposure and health is also increasing in the world. There are substantial literatures about effects of O_3 exposure on public health especially for respiratory diseases (14; 26). Adverse health effects were observed in asthma patients under O_3 exposure.

Hospital admission and emergency visits for respiratory diseases were found to be associated with O_3 exposure. With completed measurements data of air pollutants, Peel et al. conducted an study to find the association of O_3 exposure and respiratory outcomes (11), and a positive association was found in the O_3 exposure and upper respiratory infections. Other studies had similar results in O_3 exposure and respiratory diseases in asthma (10; 14) and chronic obstructive pulmonary diseases (10) that provided supportive evidences on the association that O_3 exposure induced adverse effects on pulmonary diseases.

O_3 exposure has been associated with total (8) and respiratory mortality (9). A cohort study conducted by Jerrett et al. exploited the association between O_3 exposure

and cardiopulmonary mortality (9). They found out that the relative risk of respiratory diseases death from O_3 exposure was 1.040 (95% CI: 1.010, 1.067).

The association between O_3 exposure and cardiovascular disease remains unclear. Several studies have reported increased O_3 level was associated with CVD in mortality (8; 12) (Table 1), while some didn't obtain similar associations between the two in morbidity studies (3; 4) (Table 2).

Table 1 Literature Reviews of Positive Associations between O_3 Exposure and Health Effects

Authors (year)	**Methods**	**Health outcomes**	**Exposure metrics of O_3**	**Main findings**
Bell et al. (2004) (12)	Daily death counts; Lag 0-, 1-, 2-, and 3-day; Distributed lag model (1 week)	CVD, respiratory disease and total deaths	24-hr, max 8-hr, max 1-hr (Apr.- Oct.)	O_3 exposure was associated with total and CVD mortalities; OR was higher in distributed lag model
Franklin and Schwartz (2008) (8)	Time-series study, percent increase in mortality with 10 ppb increase in O_3	Total mortality	24-hr in summer time (May to Sep.)	O_3-mortality association was found, 0.89% (95% CI, 0.45-1.33%) increase of death for per 10-ppb increase in 24-hr summertime O_3
Bell et al. (2005) (27)	Meta-analysis 0-, 1-, and 2-day lag	Total and CVD deaths	N/A	An association between short-term exposure to O_3 and mortality was found.
Ito et al. (2005) (28)	Meta-analysis Lags up to 3 days	Nonaccidential mortality	N/A	An association between short-term O_3 exposure and mortality was collectively suggested.

Zanobetti et al. (2002) (29)	Time-series study design Lag 0 Average 0-1 lag Sum 0-20 days lag, unconstrained/ penalised	Total mortality, CVD and respiratory deaths	Max 8-hr mean	Total, CVD, and respiratory deaths were associated with O_3 exposure
Lee et al. (2008) (30)	Case-crossover 2-day moving average	Hospital admission for CHF	Daily average	An association between O_3 and CHF with DM admissions was found

Table 2Literature Reviews of Negative Associations between O_3 Exposure and Health Effects

Authors (year)	**Methods**	**Health outcomes**	**Exposure metrics of O_3**	**Main findings**
Forastiere et al. (2005) (31)	0-3 lags (single day) 0-1 lag (moving average)	Coronary death	Max 8-hr mean	Coronary deaths were not associated with O_3 exposure
Liang et al. (2009) (32)	Time-series study Summer/ winter 5 days lag 5 days moving average	Total mortality, CVD and respiratory deaths	Max 8-hr (9am to 5 pm) 24-hr	O_3 exposure was not associated with daily mortality from respiratory and CVD
Medina-Ramon et al. (2008) (13)	Case-only study design Lag 0-2 (from JAMA)	Respiratory disease, CVD, diabetes deaths	Mean O_3 level	No significant association between DM death and O_3 exposure was found
Stieb et al. (2009) (10)	0-, 1-, 2-day lag	Emergency department visits including angina, myocardial infarction,	Daily average 3-hr average	No association between cardiopulmonary emergency visits and O_3 exposure was

		heart failure and dysrhythmia		observed
Zanobetti and Schwartz (2006) (3)	Lag 0 0-1 days mean	Hospital admission for myocardial infarction and pneumonia	N/A	Association was not observed in O_3 exposure and CVD admissions

2.1.3 Air pollution and susceptible groups

Previous studies have shown that the associations between air pollutants and cardiopulmonary diseases are prominent in the susceptible groups such as elderly (13), asthmatics (14), those with cardiopulmonary disease (15), and diabetics (16-18).

Diabetics are more susceptible to ambient particles on mortality and daily hospital admissions. Zanobetti et al. found that CVD patients with diabetes were at higher risk in hospital admission than CVD patients without DM diagnosed (18). PM exposure was associated with vascular reactivity impairment and endothelial dysfunction in diabetes patients (33), and inflammation makers increased in diabetics exposed to $PM_{2.5}$ (34).

2.2 Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease accounting for more than 3 million deaths in the world each year according to World Health Organization (WHO). It has become one of the top ten leading causes of death in many countries around the world.

Diabetes is a risk factor of CVD (35), and patients with DM diagnosed were at higher level of oxidative stress (36). Some studies showed that inflammation in diabetics were associated with air pollutants (19; 37). In the previous study, CVD patients with DM were found more vulnerable than those without DM (16). Another study also reported the risk of O3 exposure were higher in DM deaths than in total and CVD deaths (23).

2.3 National Mortality Registry

Mortality data has been applied in population-oriented studies for years, there were researches estimated the percentage change of daily deaths per unit increase of air pollutants such as PM_{10} or O_3 (7; 38-40). In Taiwan, mortality database was based on

the household registry system. Some databases in Taiwan are based on the household registry system including the National Registry Mortality database and the National Health Insurance database. The registry address is not equal to the living address, but in sum, more than 90% people live in the registry address in Taiwan (41).

The National Registry Mortality database offers information including the identification number, the date of death, the place of death, and the cause of death of deceased person. Only underlying cause of death from the death certification will be recorded in mortality database, and the accuracy of cause selection effects the statistic results (42). In Taiwan, the agreements of mortality data and death certifications are higher than 60% (43; 44), and diseases which are the underlying cause of death but not a fatal cause , for instance, diabetes, may not be mentioned in the death certifications leading to the underestimate of certain cause of death (42). However, the percentage of diabetes mentioned was similar with other countries (45), thus the bias of underlying cause of death selection was limited.

2.4 Case-crossover study design

Case-crossover has been used in the studies of air pollution and health effects for decades (46). It's a study design combined with crossover and case-control study designs(47) that all participants in the study are defined as cases and controls. The period of event defined in the study will be selected as risk or hazard period, and the period without onset will be identified as referenced or control period. With this classification, researchers are able to exploit the differences between the event and non-event. This study design has been well applied in investigating the association between air pollution and acute health effects from mortality (6; 48; 49) and morbidity (3; 50) to explore the risk of short-term effect on health outcomes. The entire cases in

the study act as their own controls, and this is the main advantage of this study design that some individual variables such as smoking status will be well matched by study design instead of statistic control. Hence, the way to select risk and referenced periods is important that some researches focused on the selection with limited bias (51-54).

Chapter 3 Material and Method

3.1 Health data

In this study, we used mortality data to examine the association between air pollutants and mortality in the general population and in patients with CVD or DM. deaths associated with diabetes (International Classification of Diseases, 9th revision (ICD-9): 250) in patients older than 50 years of age in metropolitan Taipei (Figure 2(A)., colored positions), Taiwan (Figure 2(B).), between 2006 and 2008 were first chosen from the National Mortality Registry, and accidental deaths were excluded. For comparison, we then randomly selected deaths in the general population (at a 1:2 ratio) and those associated with CVD (ICD-9: 390- 459; at a 1:2 ratio) that were matched according to gender and age in the same study area from 2006 to 2008 with the DM deaths. Accidental deaths were not included in the total mortality group in our study.

3.2 Environmental data

Air pollutant levels were collected from the Taiwan Air Quality Monitoring Network, Environmental Protection Administration (EPA), Taiwan (http://taqm.epa.gov.tw/taqm/en/PsiAreaHourly.aspx). The study was conducted in metropolitan Taipei, including Taipei City and part of Taipei County within the Taipei Basin, where 15 monitoring stations are located. Daily averages of temperature, relative humidity (RH), carbon monoxide (CO), sulfate dioxide (SO_2), nitrogen monoxide (NO), nitrogen dioxide (NO_2), Nitrous Oxides (NO_X), O_3, particulate matter which aerodynamic diameter less than 2.5μm ($PM_{2.5}$) and 10μm (PM_{10}) were calculated. The Pearson coefficients of environmental data from different monitoring stations are highly correlated, and the averages of 15 monitoring stations were therefore used in this study

to represent daily exposure concentrations of cases during and before their deaths. In addition, we applied the daily 8-hour maximum concentration for analysis, which was used according to WHO air quality guidelines and regulations (55). $PM_{2.5}$ was not measured until August 2005 in Taiwan. We therefore collected data from 2006 to 2008 at 15 stations in metropolitan Taipei, Taiwan (Figure 2(B)., dots).

3.3 Statistical analysis

In the present study, a case-crossover design was applied to examine the association between exposure to ambient air pollutants and total mortality, and mortality caused by either CVD or DM. This is a mix of case-control and crossover designs in which cases act as their own controls, and it is also able to compare each subject's exposure between the event and non-event. In our study, the event is defined as risk period, and the non-event is defined as reference period. Case-crossover designs are able to control confounder effects such as gender, age, and other time-varying factors (47; 56) by study design rather than statistical models.

Moving average and single-lag models were used to investigate the effects of air pollutant exposure. Days 0 to 6 before the death were selected as the risk period. In the moving average model (Figure. 3), the exposure concentrations were computed with moving averages of 1-day (the day of death) to 7-day (the day of death to six days before death) to examine the risk of air pollutant exposure on mortality. In the single-lag model, every single day before death from 0-day (0-day lag) to 6-day (6-day lag) was selected as the risk period.

Four reference periods were selected every 7 days before death for 1 month (i.e., 7, 14, 21 and 28 days) before the risk period to control the day of the week, to remove trend effects, and to minimize the bias of selection (57) (Figure. 3). The concentrations

of reference periods were calculated the in same manner as the risk periods in the same model.

The effects of PM_{10} and $PM_{2.5}$ were adjusted in the models separately. In this study, interquartile range (IQR, 75%- 25%) concentrations, which was calculated between 2006 and 2008, were used to express odds ratio (OR) estimations after modeling. Conditional logistic regression model (PROC LOGISTIC) was applied to calculate the OR between risk and reference periods with SAS 9.1.3. Relative humidity and temperature were included in the final models.

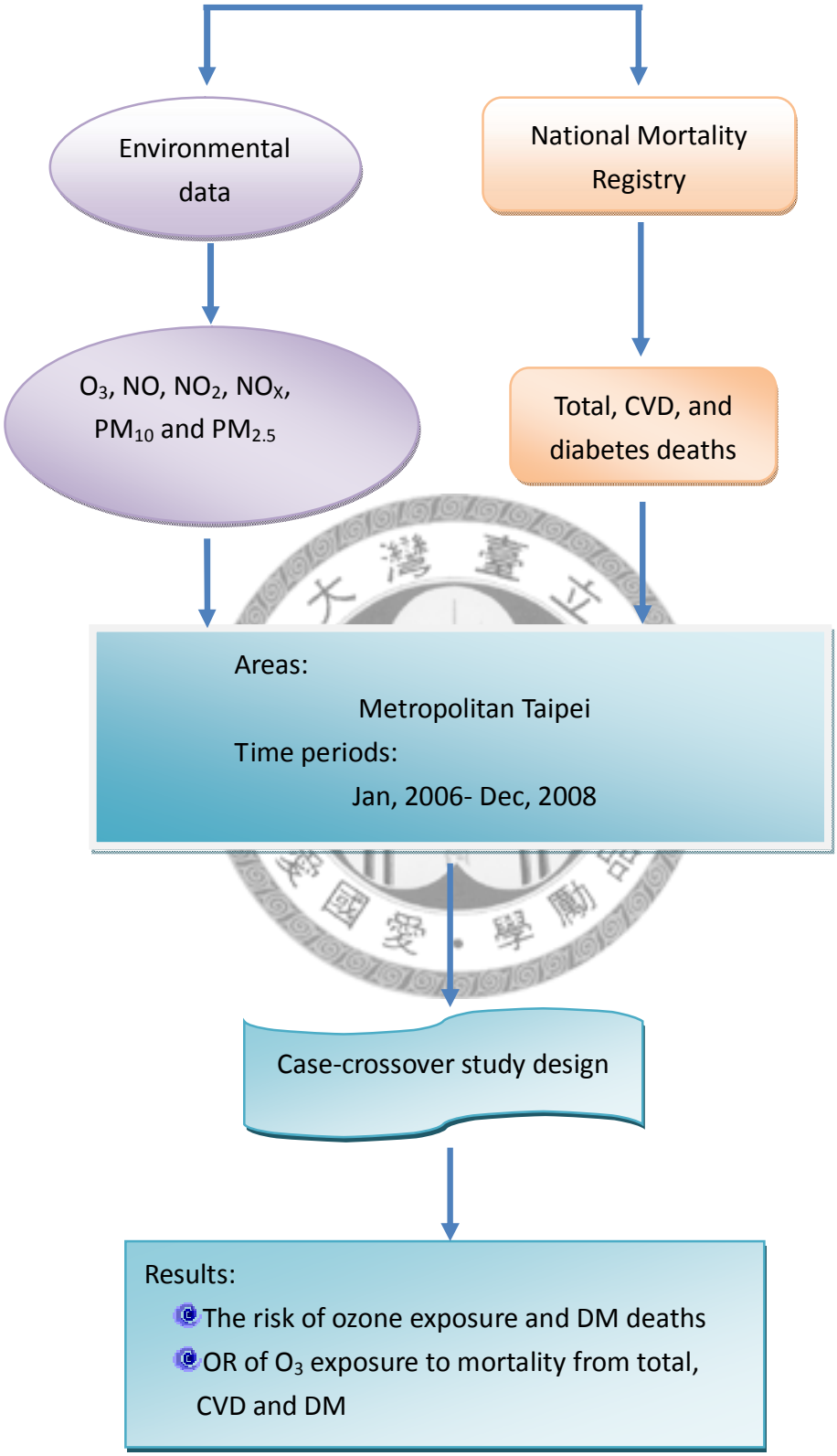


Figure 1. The flowchart of the present study design.

Chapter 4 Results

The demographic distribution of total, CVD, and DM deaths in metropolitan Taipei between 2006 and 2008 is shown in Table 3. There are significant differences in age distribution. The environmental data, including temperature, RH, PM_{10}, $PM_{2.5}$ and daily and maximum 8-hour mean O_3 levels, are shown in Table 4. To construct 2-pollutant models, correlations between air pollutants were computed (Table 5), and only PM_{10} and $PM_{2.5}$ were highly correlated.

Moving averages from 1-day to 7-day were computed. There was an increased risk of O_3 exposure on DM mortality from the 1-day up to 7-day moving averages in the single pollutant model (Figure 4.). A similar pattern was observed for the maximum 8-hour mean of O_3, with less significant results than the daily average of O_3. Effects of PM_{10}, $PM_{2.5}$, NO, NO_2 and NO_X were not observed in our study.

We observed a significant risk (7-day OR= 1.08, 95% confidence interval (CI): 1.03, 1.15, adjusted by $PM_{2.5}$) of O_3 exposure on DM mortality with the moving average model (Figure 5.) adjusted by PM_{10} or $PM_{2.5}$. Similar results were observed when the maximum 8-hour O_3 concentration was used (7-day OR=1.08, 95% CI: 1.03, 1.13, adjusted by $PM_{2.5}$) (Figure 6.). In the single-lag model, we observed two peaks in both daily (Figure 7.) and maximum 8-hour (Figure 8.) O_3 metrics. However, the effects were less prominent than those in the moving average model.

Mortality risks due to O_3 exposure for different subgroups were further assessed using the daily moving average model (Figure 9. and 10.) and the single-lag model (Figure 11. and 12.). An association between O_3 exposure and mortality was found in the daily moving average model for males (7-day OR=1.19, 95% CI: 1.07, 1.33, adjusted by $PM_{2.5}$), but not for females (7-day OR=1.03, 95% CI: 0.92, 1.16, adjusted

by $PM_{2.5}$). In the daily moving average model with maximum 8-hour O_3 concentrations (Figure 10.), the similar result was also observed for male (7-day OR=1.08, 95% CI: 1.03, 1.15, adjusted by $PM_{2.5}$). While in the single-lag model with daily (Figure 11.) and maximum 8-hour (Figure 12.) O_3 concentrations, the effects of O_3 exposure on mortality by different genders were not found (male, 7-day OR= 1.06, 95% CI: 0.99, 1.13; female, 7-day OR= 0.99, 95% CI: 0.92, 1.06; adjusted by $PM_{2.5}$ with daily O_3 concentration). The age group of 50-65 years in the moving average model had an elevated risk (7-day OR=1.22, 95% CI: 1.02, 1.46, adjusted by $PM_{2.5}$) of O_3 exposure (Figure 13.), whereas we did not observed any significant results in the groups greater than 66 years old. In the moving average model with maximum 8-hour O_3 concentrations (Figure 14.), we did not observe prominent results in different age groups, neither in the single-lag model with daily and maximum 8-hour O_3 concentrations (Figure 15. and 16.).

We further compared the OR of O_3 exposure and total mortality, CVD deaths and DM deaths. In the daily moving average model, similar patterns of cumulative effects of risk between O_3 exposure and mortality were found for total (7-day OR= 1.17, 95% CI: 1.10, 1.24, adjusted by $PM_{2.5}$) and CVD (7-day OR= 1.10, 95% CI: 1.04, 1.16, adjusted by $PM_{2.5}$) mortalities (Figure 17.). It appears that DM deaths are not at higher risk than total and CVD deaths of O_3 exposure. According to the 7-day OR results, males have a higher association from O_3 exposed in total (7-day OR= 1.16, 95% CI: 1.07, 1.26, $PM_{2.5}$ adjusted), CVD (7-day OR= 1.15, 95% CI: 1.06, 1.24, $PM_{2.5}$ adjusted) and DM mortalities (Figure 18.). In contrast, for females, we only observed increased risk with total mortality (7-day OR=1.18, 95% CI: 1.09, 1.28, $PM_{2.5}$ adjusted). The age groups between 50-65 years were at risk for DM deaths, while groups older than 66 years were at risk for total and CVD deaths (Figure 19).

Chapter 5 Discussions

In this study, we found that O_3 exposure was associated with total, CVD and DM mortality, and there were cumulative effects between O_3 exposure and mortality. However, the risk of O_3 exposure on DM death is not higher than those for total and CVD deaths.

5.1 Ozone exposure and mortality

Associations between O_3 exposure and total mortality have been found in previous studies (8; 12). Meta-analysis studies have also reached the same conclusion on the association between O_3 exposure and mortality (27; 28). An association between CVD death and O_3 exposure has also been reported (58). In a study conducted by Bell et al. (12), the 7-day average O_3 concentration was associated with daily total and CVD deaths. However, other studies did not obtain consistent results on the risk of death after O_3 exposure (13; 31; 32). The association of CVD hospital admissions and O_3 exposure has not been consistently observed (3; 10). Data on the relationship between O_3 exposure and DM deaths is limited. One study found an association between DM mortality and 4-day averages of 8-hour maximum O_3 exposure (23). In other studies, an association between 8-hour daily O_3 exposure and DM mortality was not observed (13; 16). In our study, we observed an increased risk and cumulative effect on DM deaths in response to the 0- to 7-day O_3 moving average. Thus, our results provide further support for the health effects of O_3 on the mortality from total, CVD and DM. Possible explanations for O_3-related mortality include increased oxidative stress, inflammatory reactions, and autonomic control dysfunctions (59; 60).

5.2 Ozone exposure metrics

5.2.1 Daily average and maximum 8-hour means of O_3 level

Both daily averages and maximum 8-hour means were used in previous studies to represent O_3 concentrations (8; 12; 13; 23; 31; 32). However, it is not clear which value serves as a better exposure metric. In the current study, we observed similar results for both the daily averages and maximum 8-hour means on all types of mortalities. One study examined the risk in three O_3 metrics, including daily, 8-hour, and maximum 1-hr O_3 concentration, and found significant associations between O_3 exposure and total and CVD deaths with these metrics (12). One study found that the ratio between maximum 8-hour mean and daily average may vary among different cities (61). Thus, both daily averages and maximum 8-hour means of O_3 concentrations should be included in the analysis.

5.2.2 Moving average and single-lag models

One study investigated the risk of O_3 exposure on total and CVD mortalities and found that the risk of O_3 exposure on mortality was higher with the moving average model than the single-lag model (12). Another study conducted single and cumulative lag models to examine the risk of O_3 exposure on CVD deaths and did not find an association between O_3 exposure and mortality in the single-lag model (31). In our study, we have found the lag effects of O_3 exposure on DM deaths in the single-lag model. It appears that O_3 exposure has acute and lag effects. However, the daily moving average metric for O_3 is more sensitive and consistent than the single-lag model. Thus, the daily moving average metric for O_3 needs to be included in the analysis for the association between DM deaths and O_3 exposure. However, hospitalization information was not available in mortality data. Thus, increasing risk of longer exposure period may be

observed due to hospitalization period in our study.

5.3 Total, CVD, and DM mortalities

DM mortality was associated with O_3 exposure, and the primary causes of death among DM deaths from multiple causes of death database were infections, CVD, respiratory diseases, and genitourinary diseases (Figure 20.).

We did not observe an increase in DM mortalities with O_3 exposure relative to other causes of mortalities. In a study conducted by Medina et al., diabetics who were exposed to O_3 did not have a higher risk of death than those with CVD (13). One study conducted in Canada found that DM patients with co-existing diseases were more likely to be affected by O_3 (16). DM is a risk factor for CVD and is known to be associated with mortality from infectious disease, and the diseases may be exacerbated in DM patients (62). Because the Mortality Registry only has one single cause for deaths, we did not further investigate the secondary causes of deaths. The specific causes of death from diabetes need to be identified in future studies. Although we did not observe increased deaths from DM as compared to total deaths, the role of DM on total mortalities needs to be further clarified.

5.4 Gender and age differences

In the present study, males and those aged between 50- 65 exposed to O_3 had an elevated risk of death due to DM. In one review paper, the author found that males were at risk for reduced lung function after O_3 exposure (63). Gender differences were also observed in the present study, as males had an elevated risk of death after O_3 exposure. This difference may be due to different time-activity patterns between genders, as males tend to spend more time outdoors than females (64). Subjects in the age group of 50-65

years had a greater risk of DM-associated death after O_3 exposure. Again, this may be explained by the fact that the younger subjects spend more time outdoors. However, the effects of age on all mortalities and those caused by CVD or DM were inconsistent. Different pathophysiological mechanisms for these mortalities may contribute to these differences.

5.5 The National Mortality Registry data

The National Mortality Registry is based on the household registration system in Taiwan. All of the citizens in Taiwan are required to have one registered address. The potential discrepancy between the household registry address and the actual living address was estimated to be less than 5% based on the study by Hung et al. (65). Thus, the misclassification of O_3 exposure for each individual should be limited and should not affect the results. The other limitation of our study is that we used average concentrations of pollutants from monitoring stations to represent individual exposure. Because of the relatively large number of monitoring stations in the study area, we are confident that the calculated pollutant levels are not greatly deviated from the true values.

In Taiwan, diabetes is frequently recorded in part I of the death certificate, while in the United States and other countries, it is recorded in part II (45) (Figure 21.). Thus, based on this coding system, DM in Taiwan would be more likely to be selected as the underlying cause of death. Caution is required when comparing mortality studies between Taiwan and western countries.

In conclusion, we found that DM mortality was associated with O_3 exposure, but that DM deaths were not more associated with O_3 exposure than total and CVD deaths. The ole of DM on O_3-related mortality needs to be further studied.

Chapter 6 Conclusions and Recommendations

In the present study, increased mortality risk in DM is associated with O_3 exposure. Moving average model with daily O_3 exposure is an appropriate exposure metric for DM deaths. With the metric of the daily average of O_3, male and subjects aged 50- 65 are at elevated risk of death. In the comparison of different causes of death from total, CVD, and DM, there is no obvious higher risk in DM death from the others, and the specific causes of death from DM need to be identified in the future study.

To improve the exposure assessment of O_3, models for estimating the correlation between monitoring measurements and individual exposure of O_3 concentration is suggested. Further, multiple causes of death database can be applied to investigate the causes of death from DM when it is released by the Taiwan Government.

Chapter 7 References

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Table 3. Demographic Distribution of Total, CVD, and DM Death in Taipei, 2006- 2008

Variables	Total deaths No. (%)	CVD deaths No. (%)	No. of DM deaths (%)		
			Total	Male	Female
Total	11534	11534	5767	2916 (50.6)	2851 (49.4)
Age	74.8 (10.5)	74.8 (10.5)	74.8 (10.5)^	73.3 (10.7)^	76.3 (10.0)^
50-65	2320 (20.1)	2320 (20.1)	1160 (20.1)**	733 (25.1)**	427 (15.0)**
66-80	5436 (47.1)	5436 (47.1)	2718 (47.13)	1346 (46.2)	1372 (48.1)
＞81	3778 (32.8)	3778 (32.8)	1889 (32.8)	837 (28.7)	1052 (36.9)

CVD: cardiovascular disease; DM: diabetes mellitus; ** P <0.001; ^ Mean (standard deviation, SD)

Total and CVD deaths were matched by DM deaths according to gender and age at 1:2 ratio

Table 4. Distribution of Air Pollutants in Taipei between 2006 and 2008

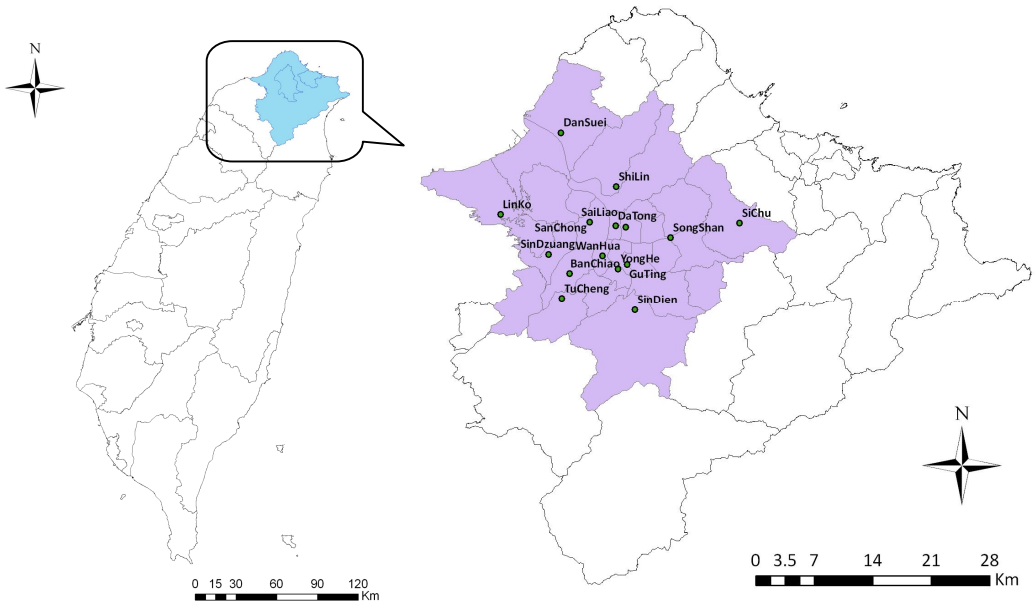
	Mean (SD)	Max	Min	IQR
Temp (℃)	23.5 (5.2)	32.3	9.3	8.5
RH (%)	72.4 (8.4)	94.5	48.0	11.9
Daily O_3 (ppb)	26.1 (8.8)	73.2	5.7	11.6
Max 8-hour O_3 (ppb)	40.6 (14.8)	105.8	7.8	17.1
PM_{10} ($\mu g/m^3$)	50.9 (23.5)	195.7	12.5	27.2
$PM_{2.5}$ ($\mu g/m^3$)	29.1 (15.2)	111.7	5.9	16.7

Temp: temperature; RH: relative humidity;

Table 5. Correlation Coefficients among Different Pollutants in Taipei, 2006- 2008

	Temp.	RH	Daily O_3	Max 8-hour O_3	PM_{10}	$PM_{2.5}$
Temp	1.00	-0.14**	-0.04	0.28 **	-0.15 **	-0.12 **
RH		1.00	-0.32 **	-0.39 **	-0.36 **	-0.23 **
Daily O_3			1.00	0.73 **	0.38 **	0.34 **
Max 8-hour O_3				1.00	0.46 **	0.47 **
PM_{10}					1.00	0.93 **
$PM_{2.5}$						1.00

Temp: temperature; RH: relative humidity; ** P <0.01



(A) (B)

Figure 2. The positions of monitoring stations (dots) and selected areas (shaded area) (B) in Taiwan (A)

Reference period	Reference period	Reference period	Reference period	Risk period

Mon	Tue	Wed	Thu	Fri	Sat	Sun
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

Figure 3. The selection of risk and reference periods in the moving average model

Risk period: moving average of 1- to 7-day before the event day

Referenced period: moving average of 1- to 7-day before the risk period every 7 days

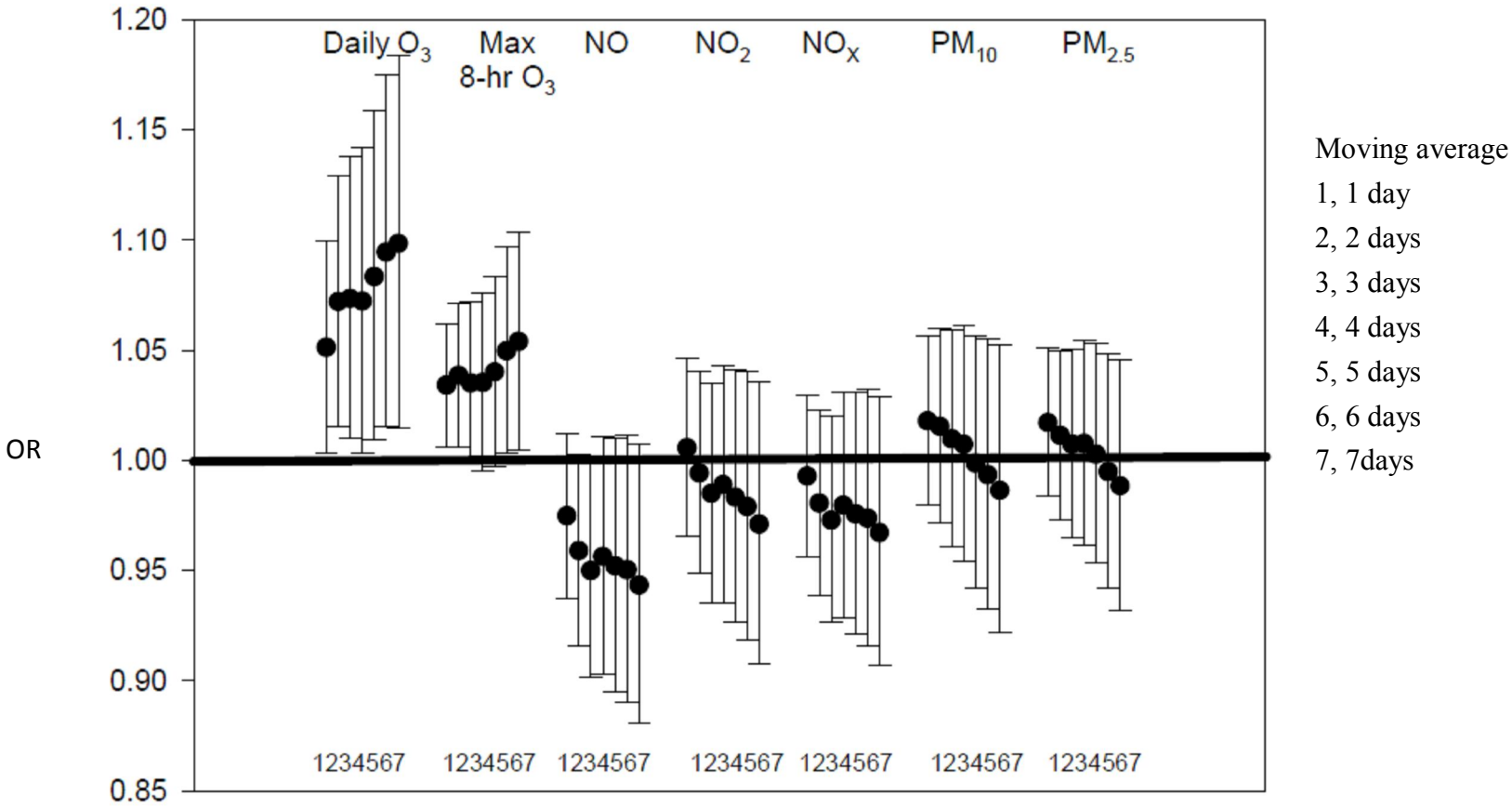


Figure 4. OR of each IQR increase among DM deaths in the moving average model.*

*adjusted by temperature and RH.

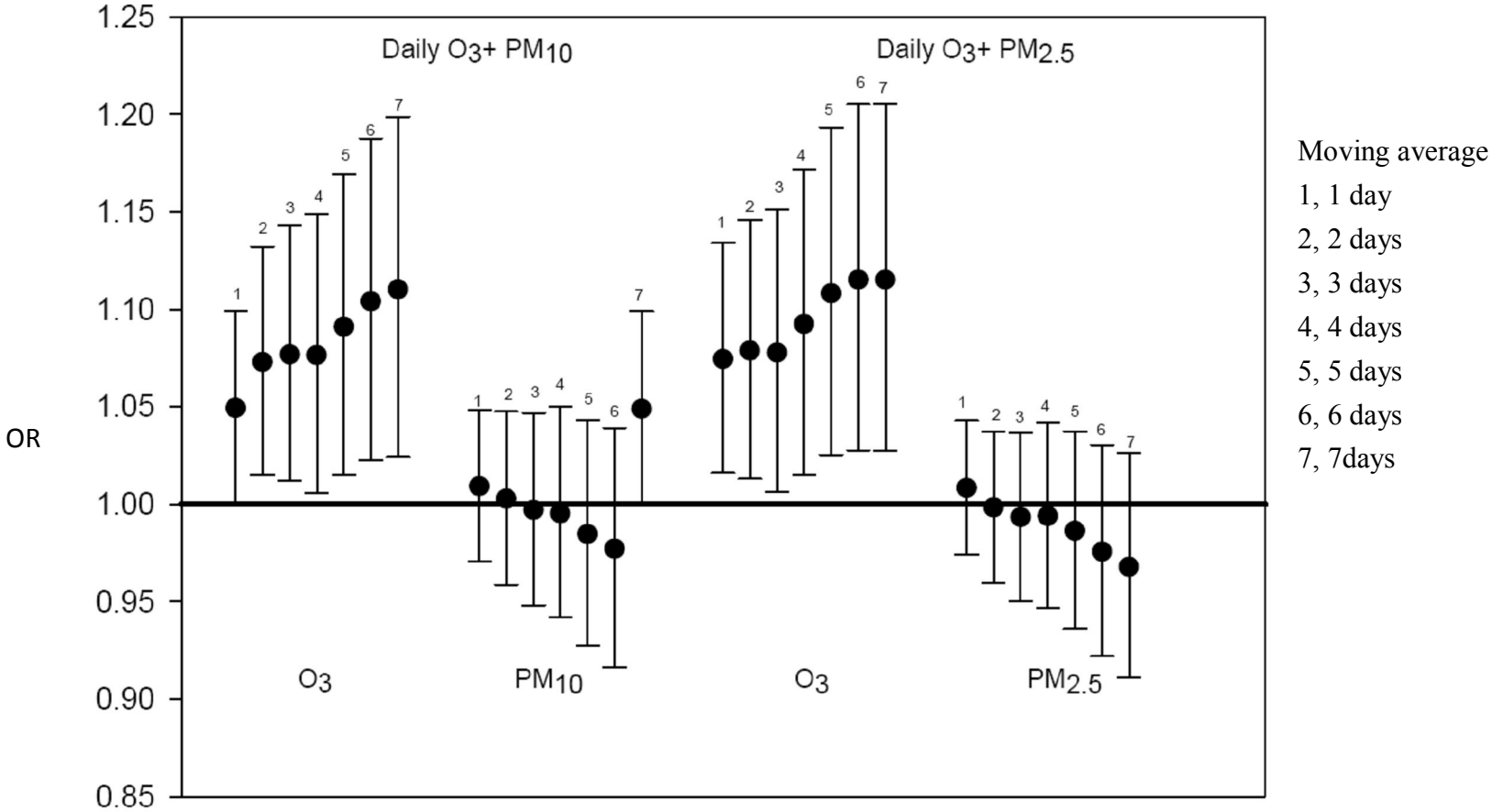


Figure 5. OR of each IQR increase among DM deaths in the moving average models** with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

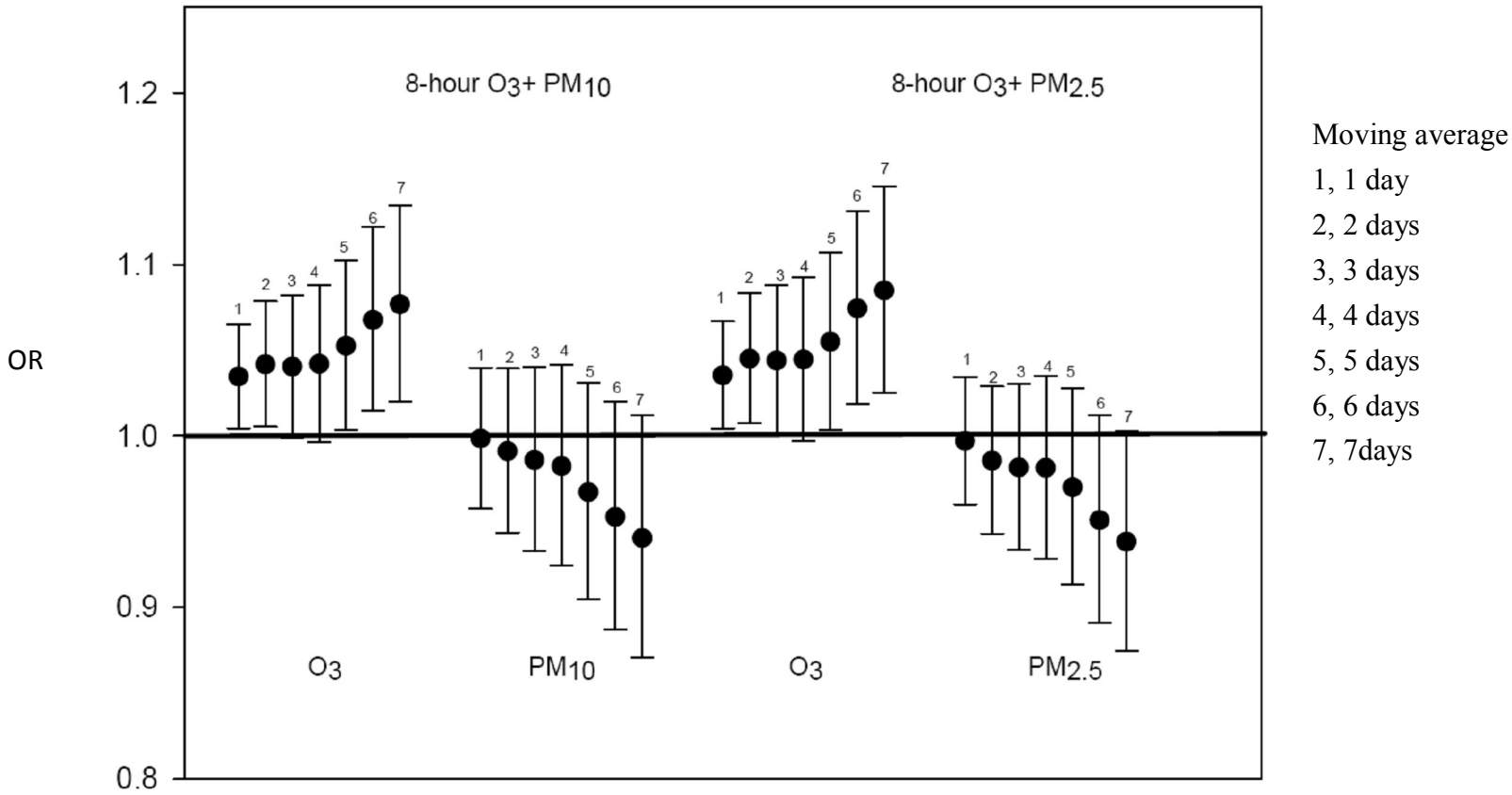


Figure 6. OR of each IQR increase among DM deaths in the moving average models** with maximum 8-hour O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

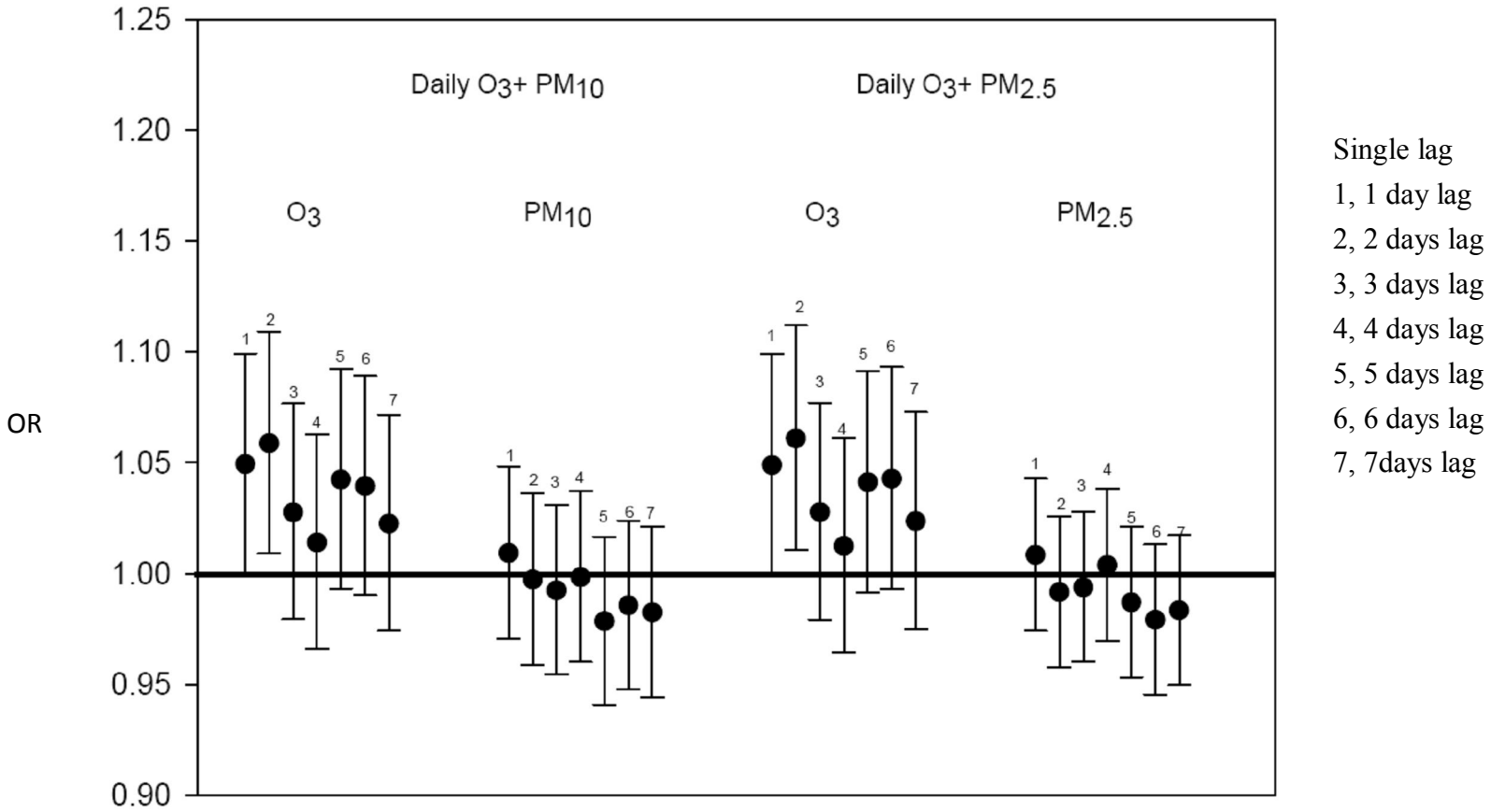


Figure 7. OR of each IQR increase among DM deaths in the single-lag model ** with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

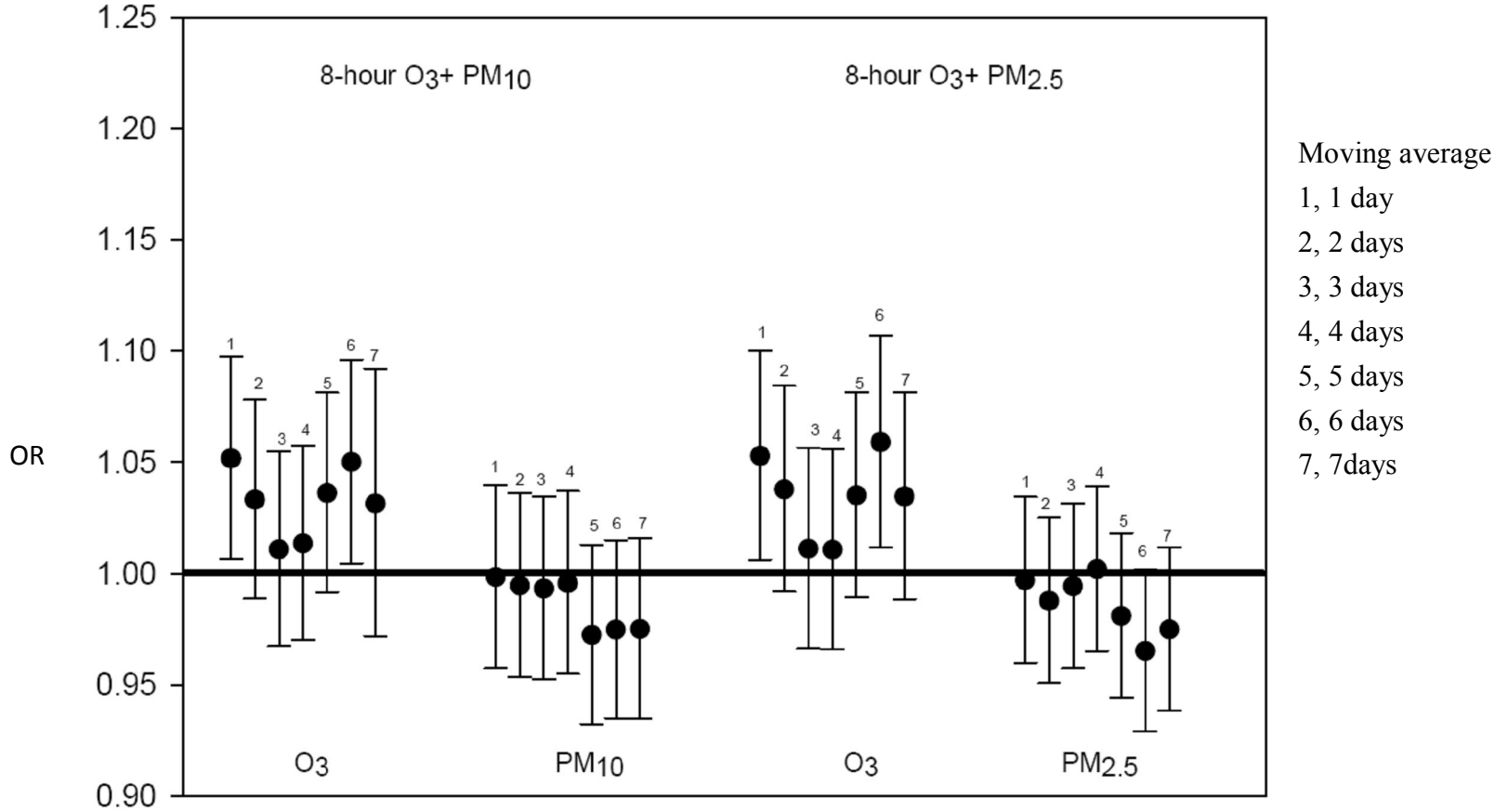


Figure 8. OR of each IQR increase among DM deaths in the single-lag model ** with maximum 8-hour O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

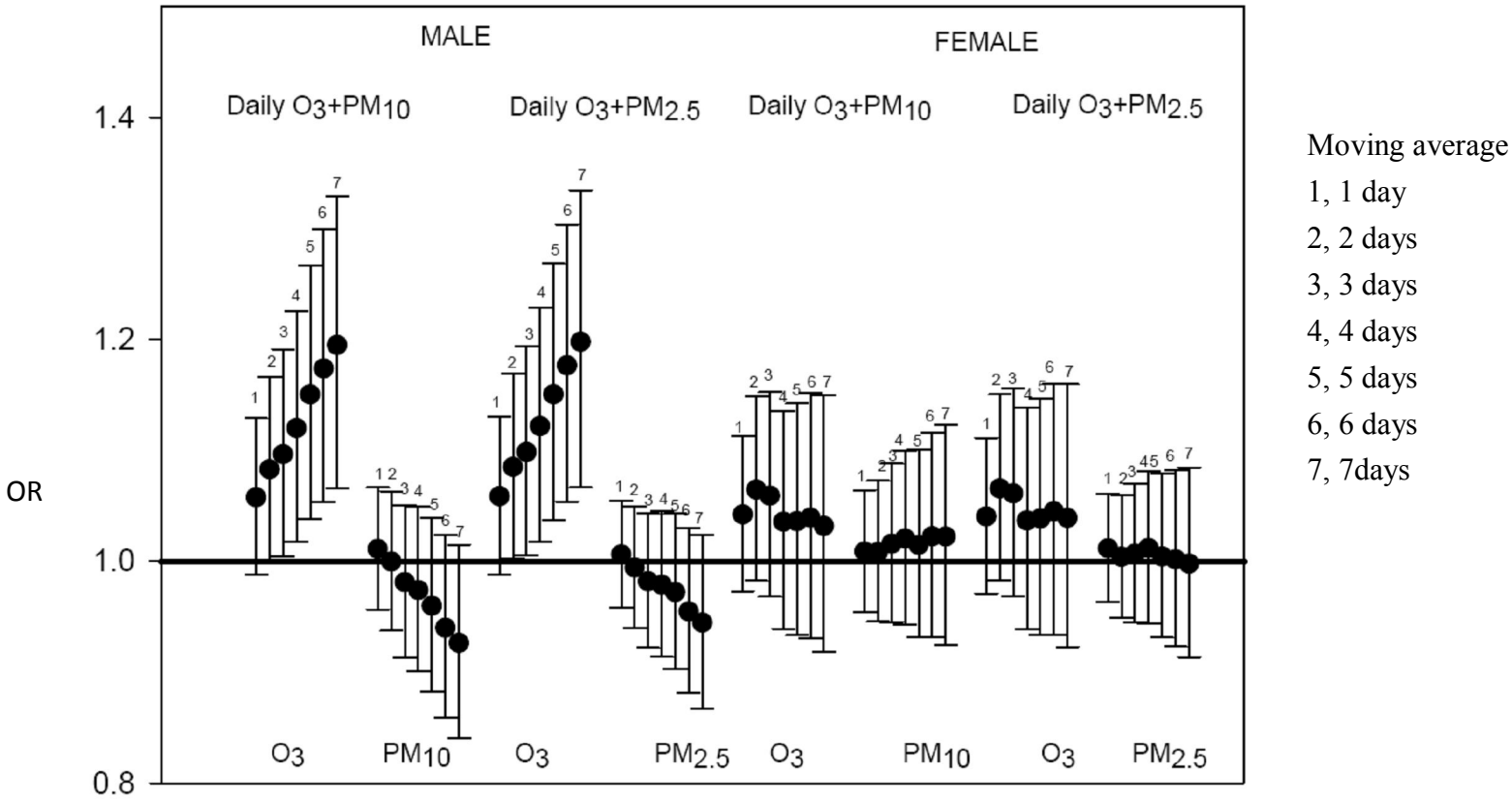


Figure 9. OR of each IQR increase among DM deaths in the moving average model** by different genders with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

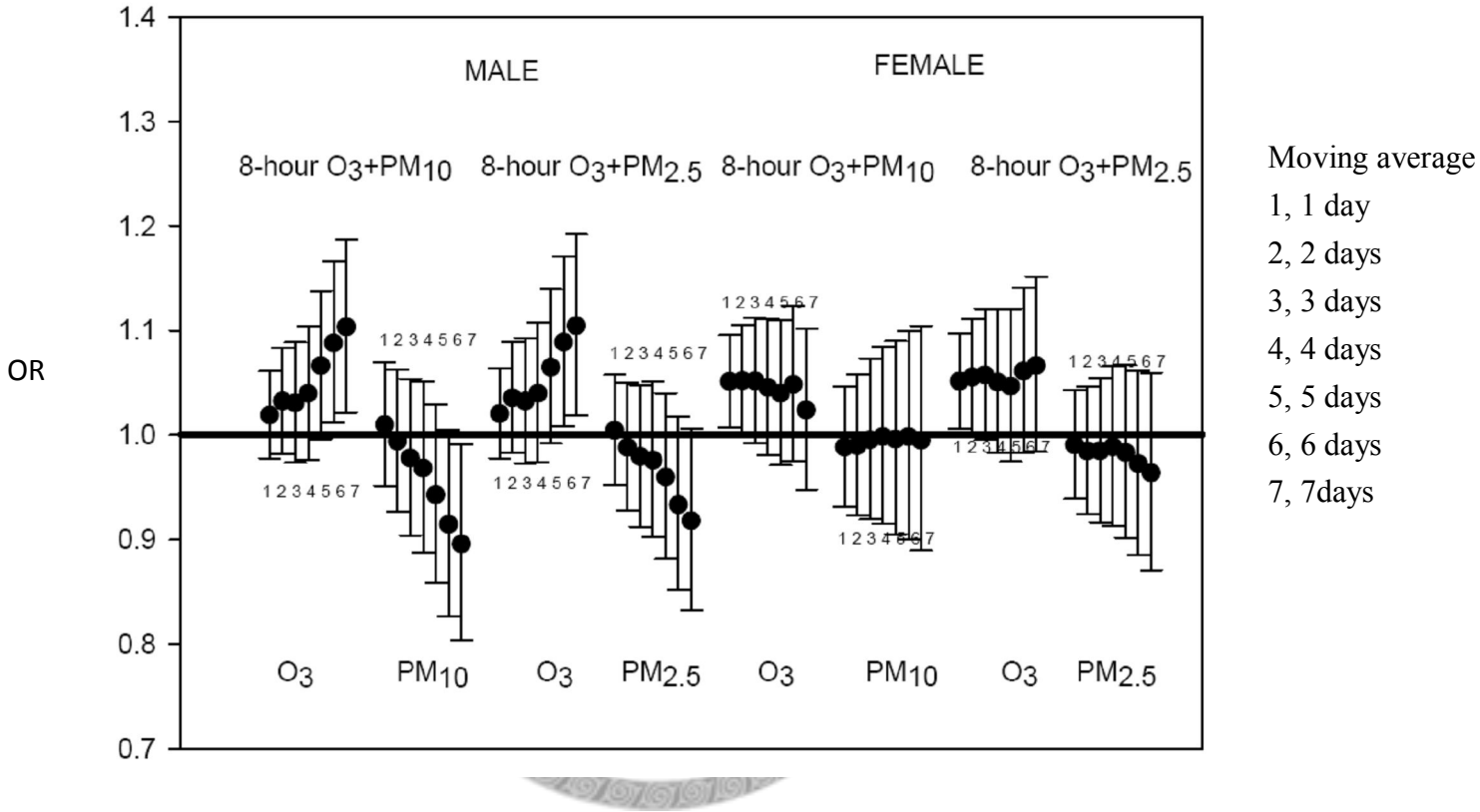


Figure 10. OR of each IQR increase among DM deaths in the moving average model** by different genders with maximum 8-hour O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

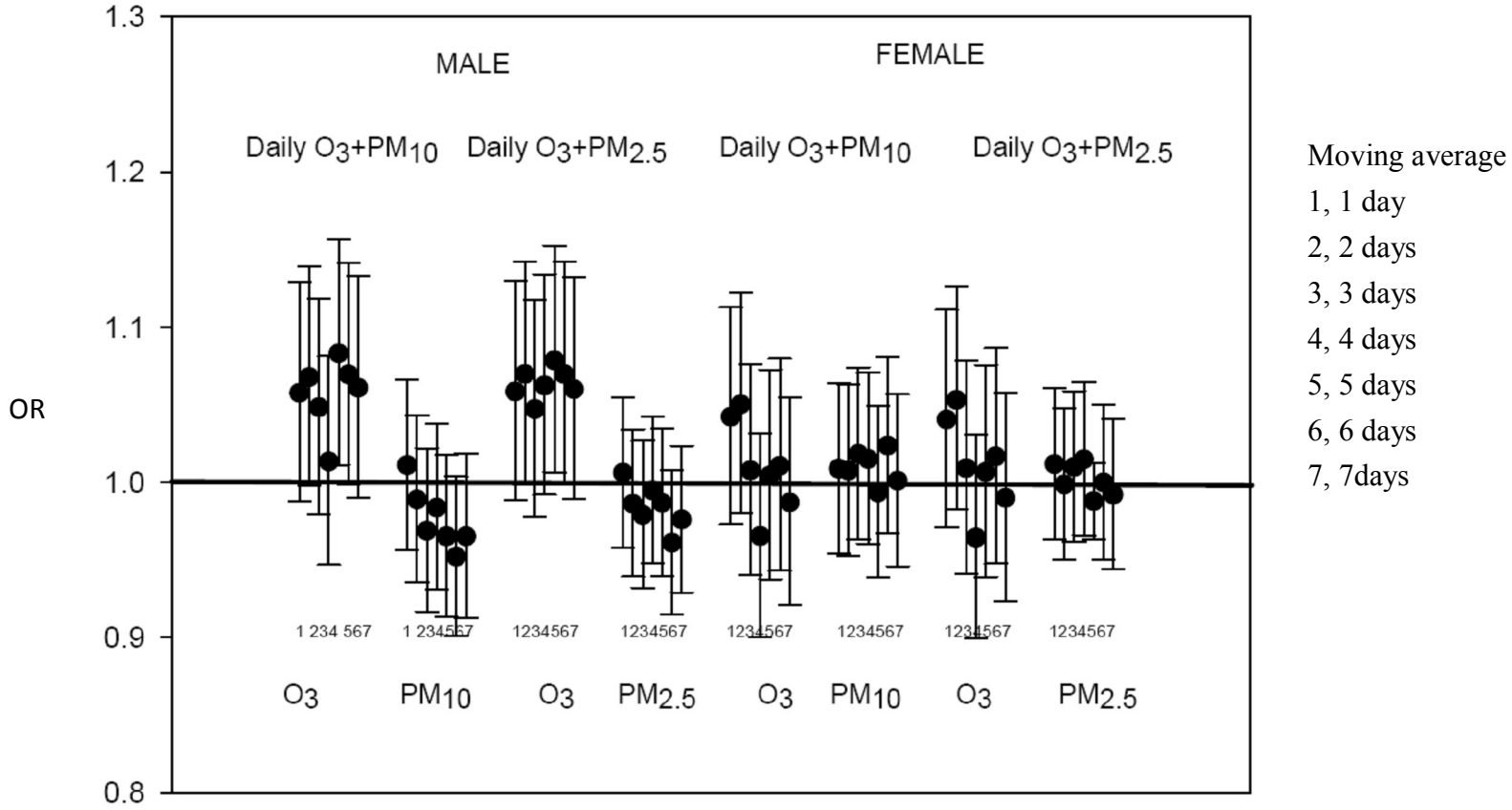


Figure 11. OR of each IQR increase among DM deaths in the single-lag model** by different genders with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

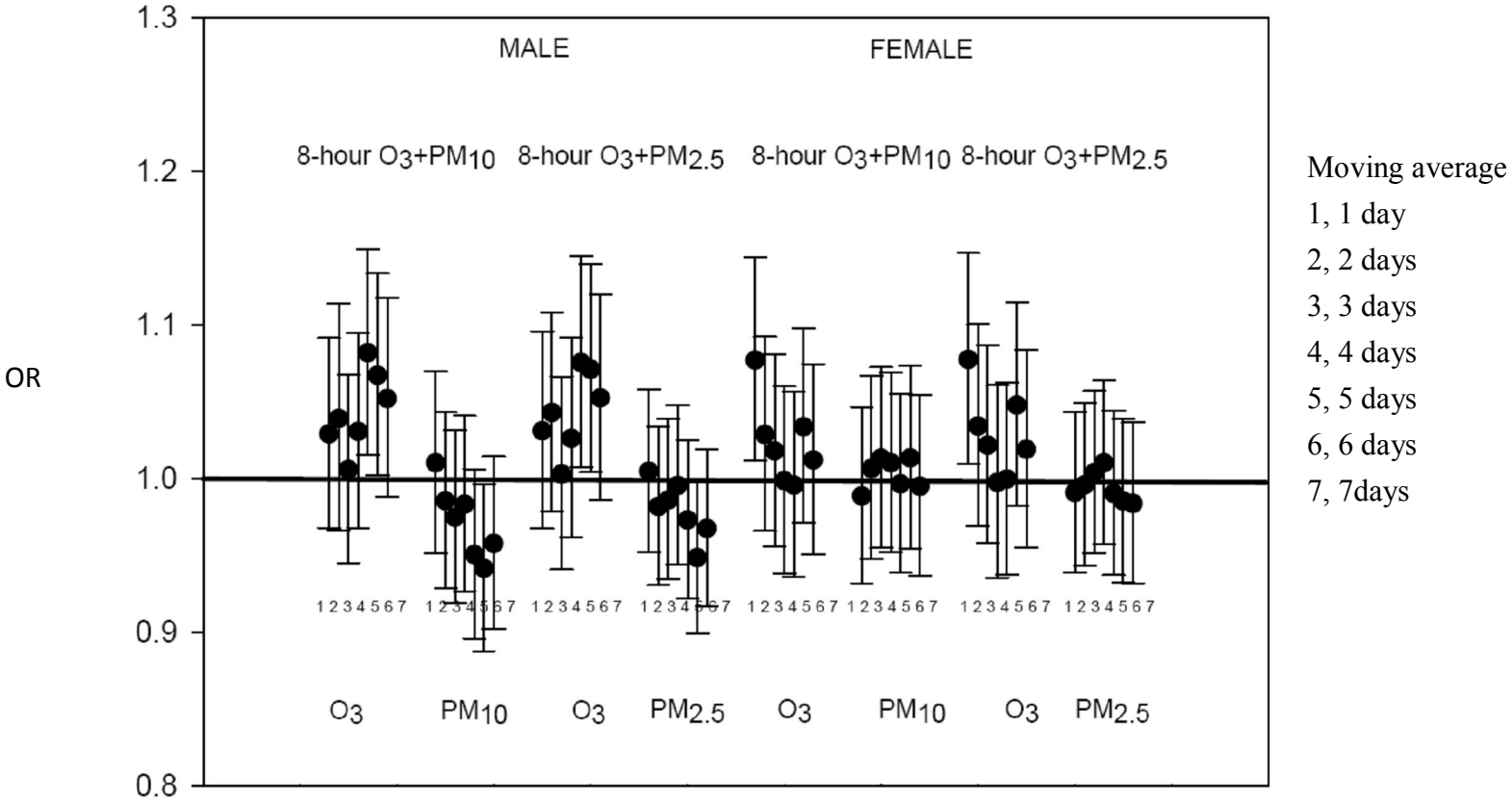


Figure 12. OR of each IQR increase among DM deaths in the single-lag model** by different genders with maximum O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

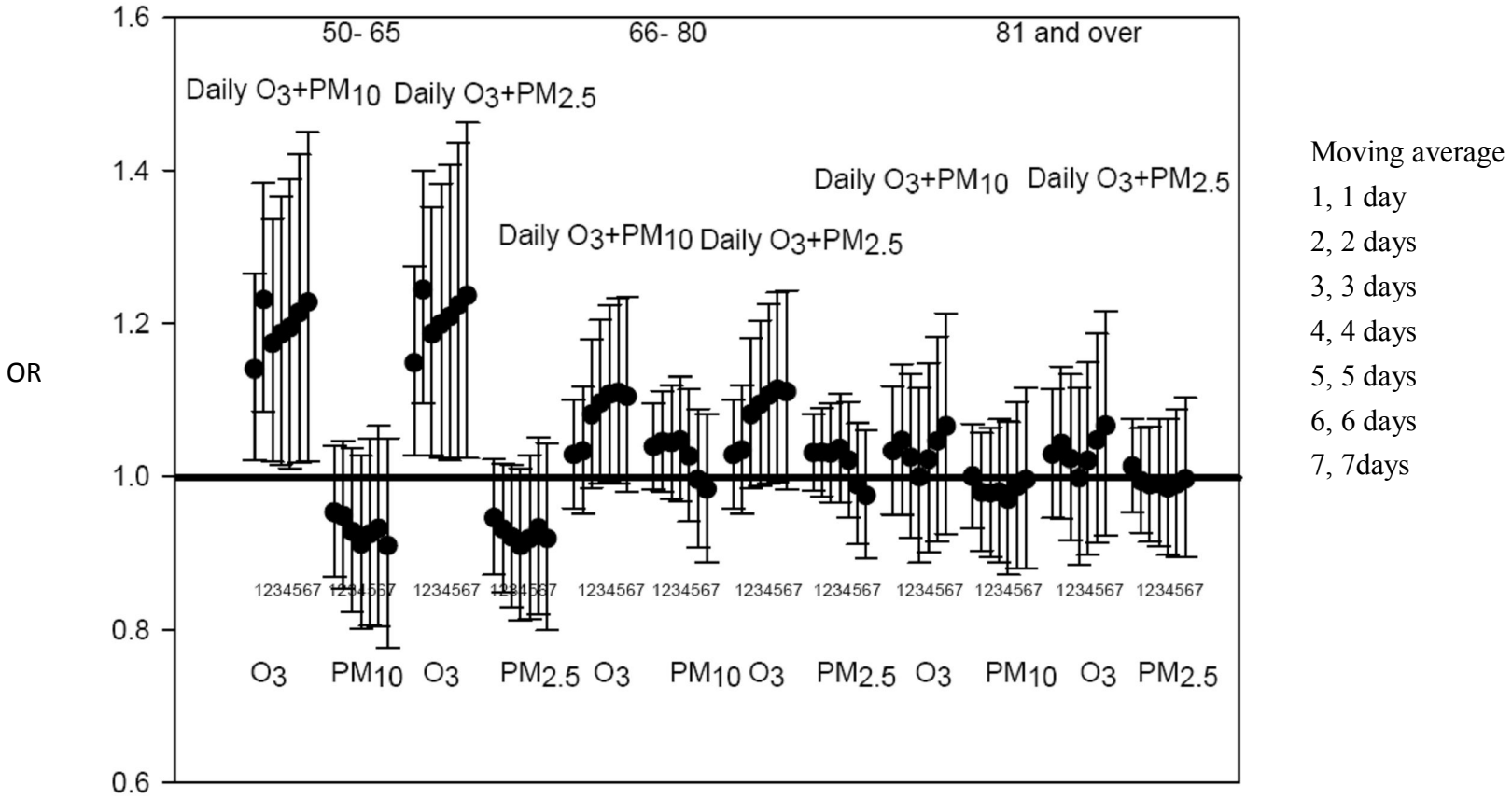


Figure 13. OR of each IQR increase among DM deaths in the moving average model** by different age groups with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

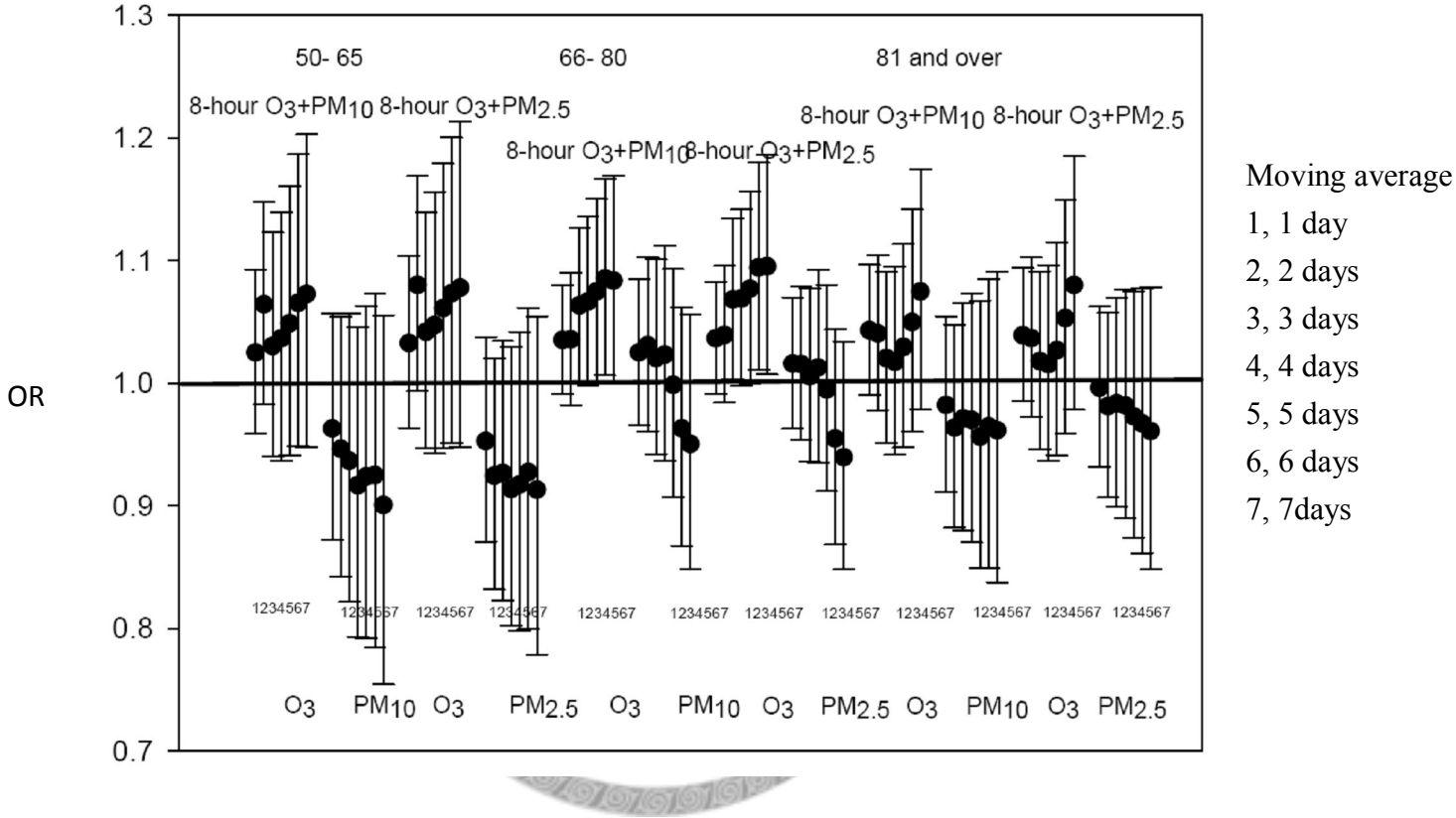


Figure 14. OR of each IQR increase among DM deaths in the moving average model** by different age groups with maximum 8-hour O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

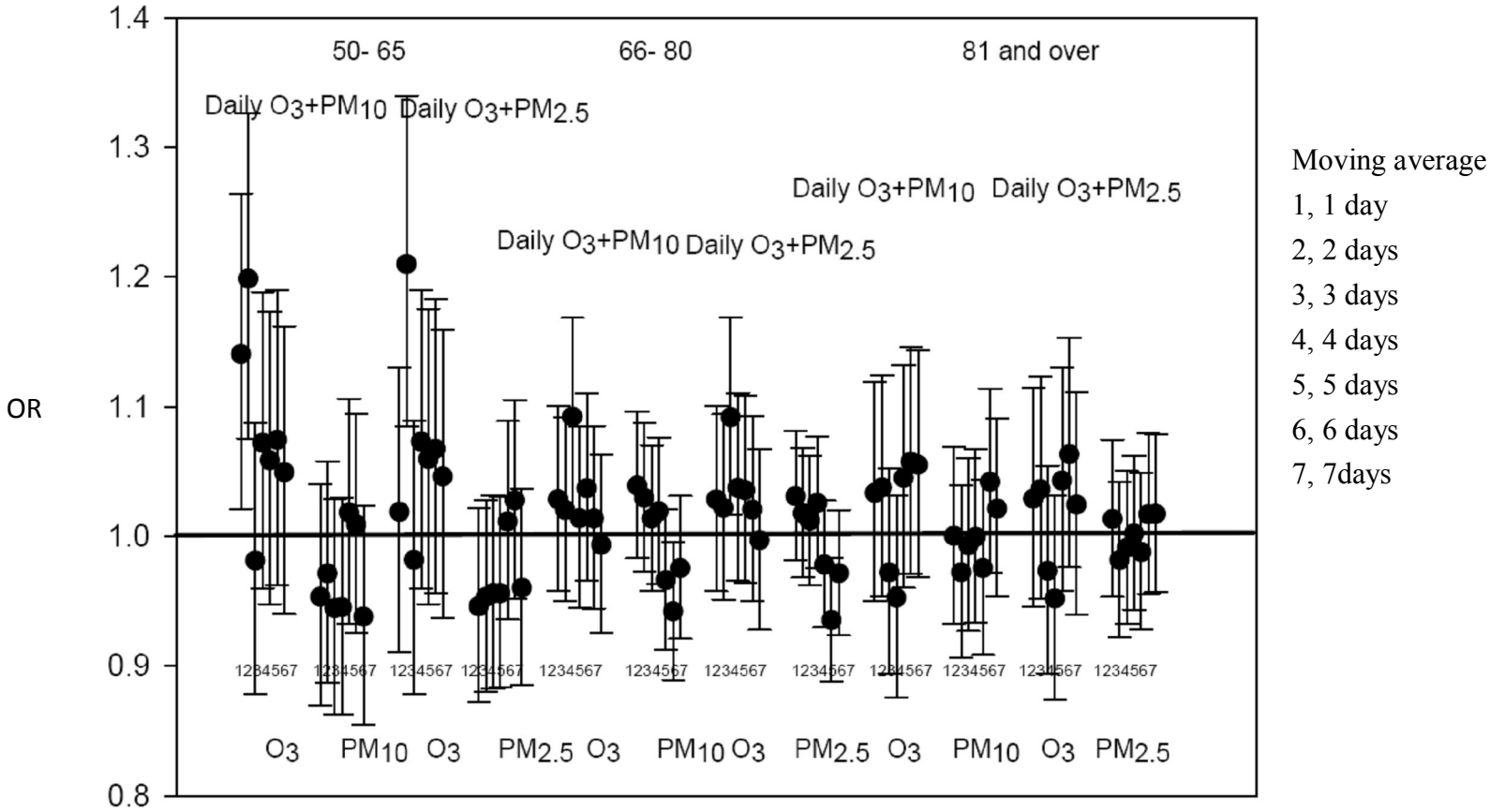


Figure 15. OR of each IQR increase among DM deaths in the single-lag model** by different age groups with daily O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

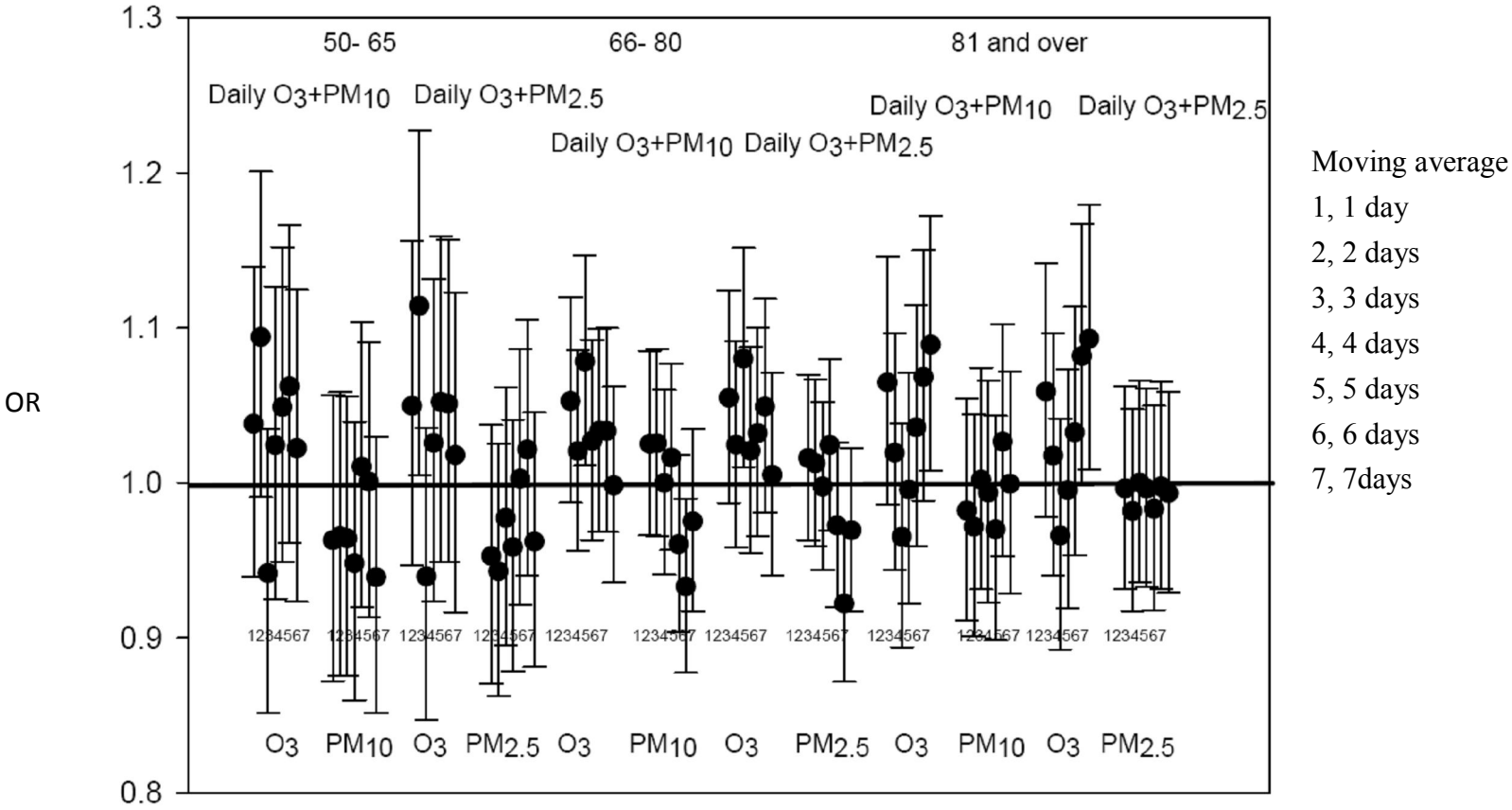


Figure 16. OR of each IQR increase among DM deaths in the single-lag model** by different age groups with maximum O_3 concentrations.

**adjusted by temperature, RH and PM_{10} or $PM_{2.5}$.

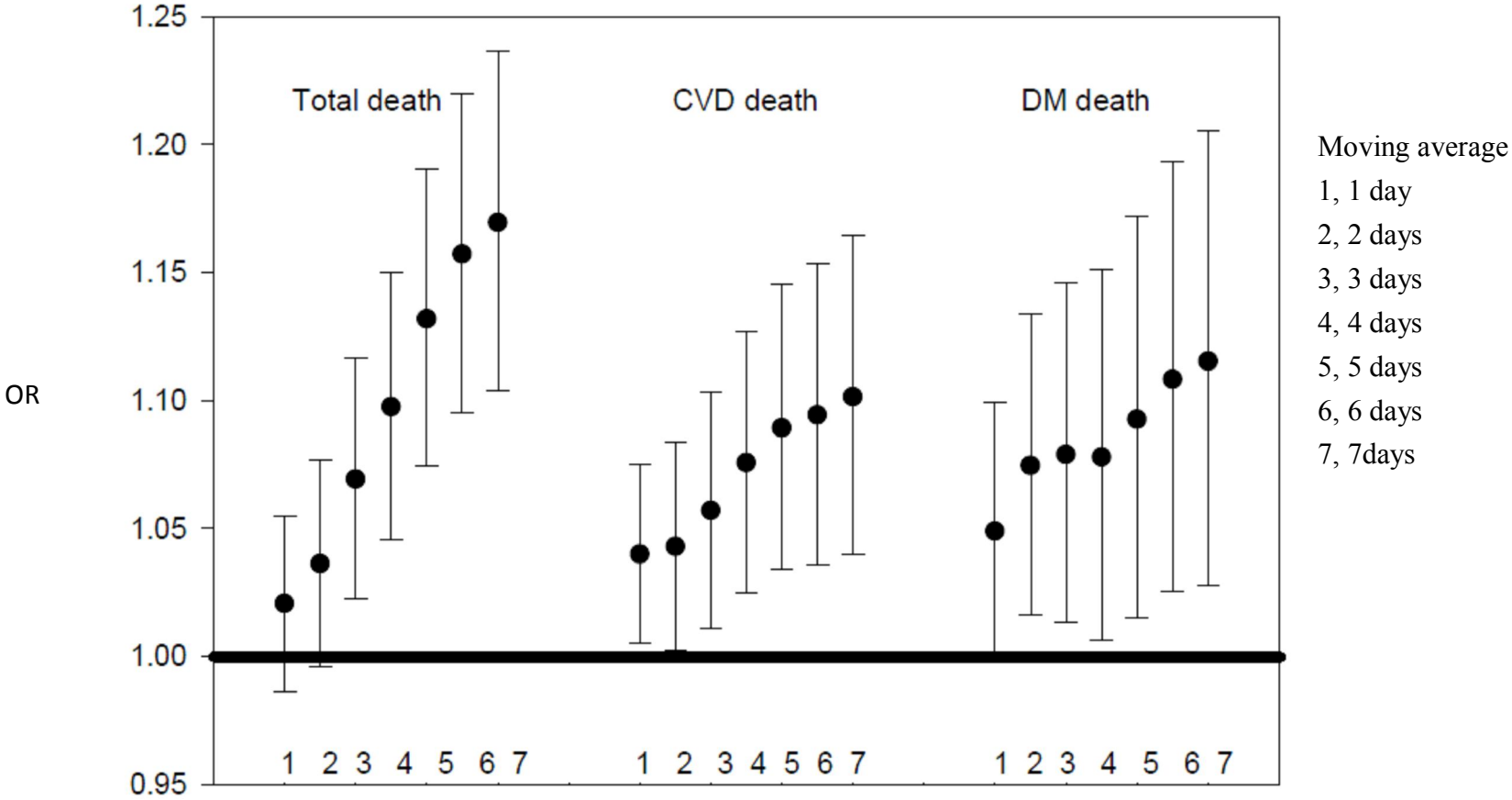


Figure 17. OR of each IQR increase in the moving average model** for total, CVD, and DM deaths with daily O_3 concentrations.

**adjusted by temperature, RH and $PM_{2.5.}$

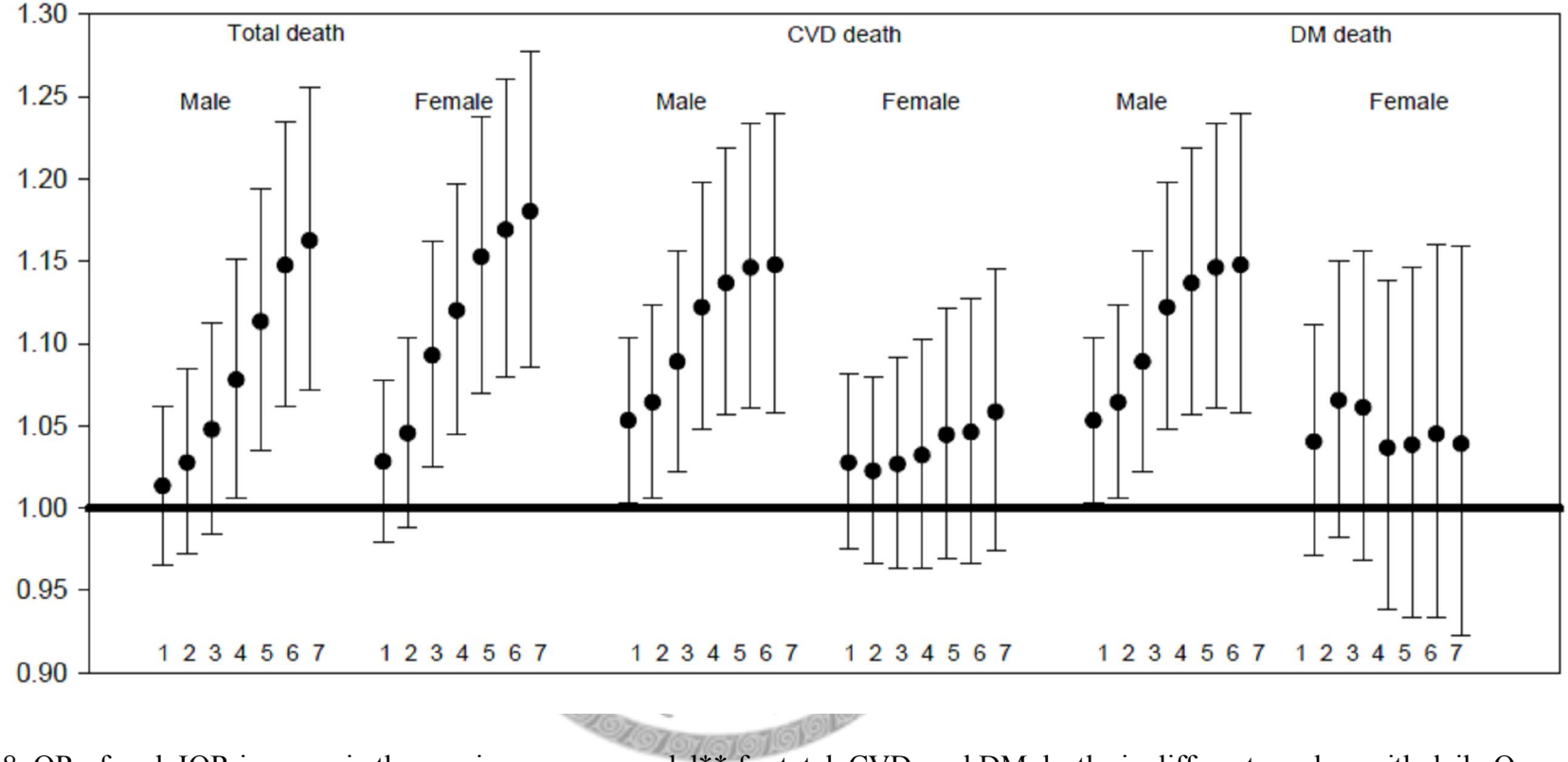


Figure 18. OR of each IQR increase in the moving average model** for total, CVD, and DM deaths in different genders with daily O_3 concentrations.

**adjusted by temperature, RH and $PM_{2.5}$.

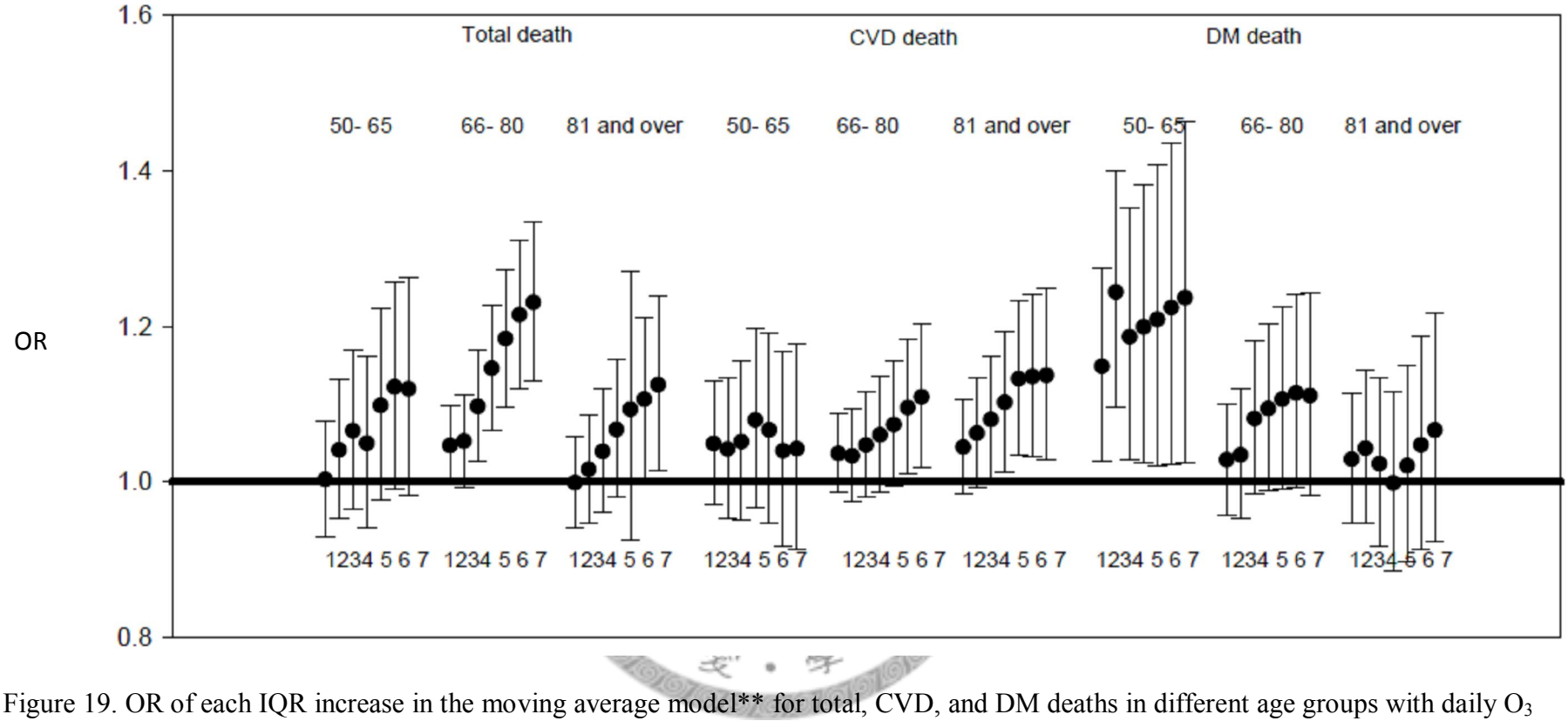


Figure 19. OR of each IQR increase in the moving average model** for total, CVD, and DM deaths in different age groups with daily O_3 concentrations.

**adjusted by temperature, RH and $PM_{2.5}$

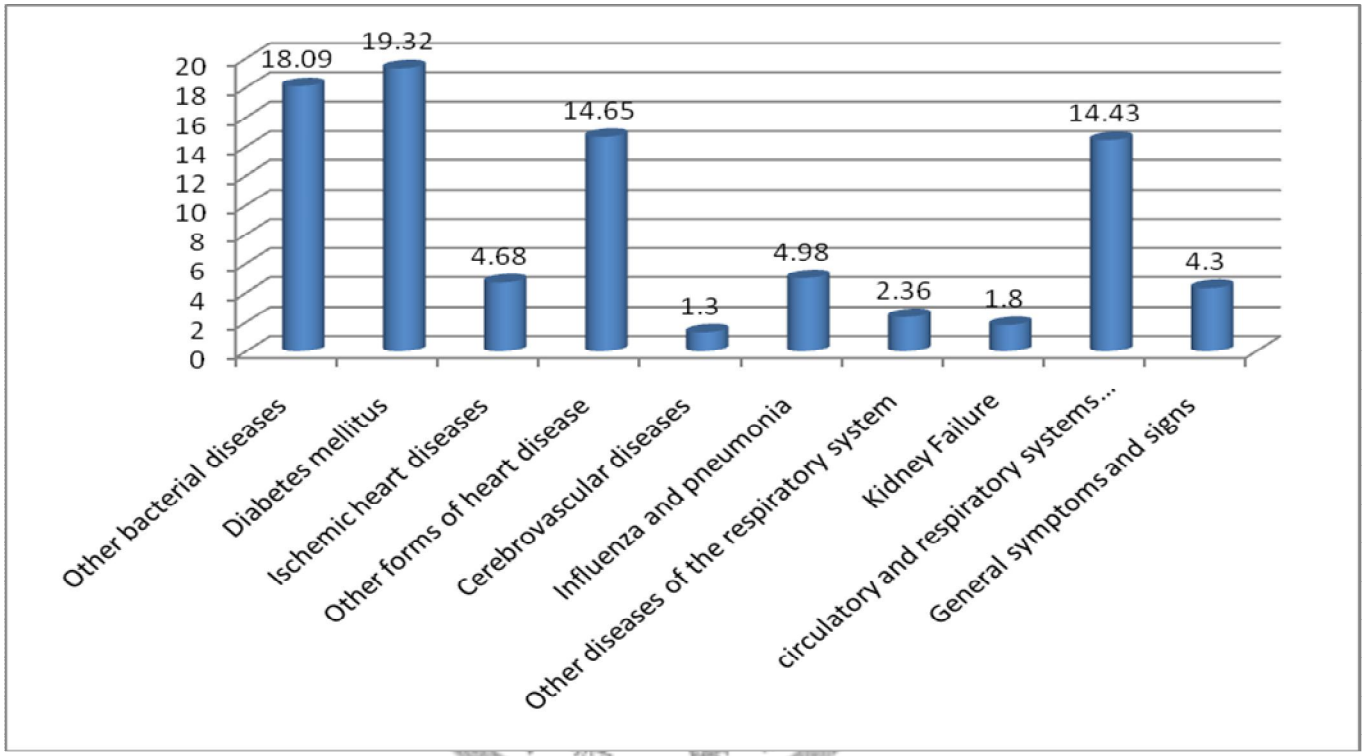


Figure 20. Primary causes of death among DM deaths from part I of the death certification

Source: Multiple Causes of Death Database, Lu.

死 亡 證 明 書

死亡證字　　號之

證明書開具單位填寫				衛生單位註碼
姓　名		性別 □男 □女	國民身分證統一號碼	
戶籍所在地	省 縣 鄉鎮 村 街 段 巷 號之 市 市 市區 里 路 弄			縣市 鄉鎮
出生年月日時	民 前□ 後□ 年 月 日 上午□ 下午□ 時 分 （出生後未滿一星期死亡者需填寫時間）			年 月 日
死亡年月日時	民國 年 月 日 上午□ 下午□ 時 分			年 月 日
死亡地點及場所	省 縣 鄉鎮 村 街 段 巷 號之 市 市 市區 里 路 弄			
	①□醫 院 ②□診 所 ③□助產所 ④□自 宅 ⑤□其 他			
死亡種類	①□病死或自然死 ②□意外死 ③□自殺 ④□他殺 ⑤□不詳			
死亡者行職業	①在何處工作從事何種行業	②擔任何種工作及職務		職業碼
死亡者婚姻狀況	①□未 婚 ②□已 婚 ③□離 婚 ④□配偶死亡 ⑤□不 詳			

死亡原因：（儘量不要填寫症狀或死亡當時之身體狀況：如心臟衰竭、身體衰弱）	發病至死亡之概略時間	原死因註碼
1.直接引起死亡之疾病或傷害： 先行原因：（若有引起上述死因之疾病或傷害） 甲、＿＿＿＿＿＿ 乙、（甲之原因）＿＿＿＿＿＿ 丙、（乙之原因）＿＿＿＿＿＿		
2.其他對於死亡有影響之疾病或身體狀況 （但與引起死亡之疾病或傷害無直接關係者）		

以上事實確無訛特此證明	診斷或證明者身分代表
醫師姓名及證書字號： 醫院（診所）名稱及開業執照字號： 醫療院所代號： 院所地址：省 縣 鄉鎮 村 街 段 巷 號之 市 市 市區 里 路 弄 中 華 民 國 年 月 日	填表人蓋章

註：死因將來如發現錯誤，惟錯誤係在當時難以避免情況下發生時，診斷者不負法律上之責任。

Figure 21. The death certification in Taiwan