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中文摘要：主旨：男性族群在心血管疾病的發生風險上明顯高於女性族群，不過，在糖尿病族群中，男女性發生心血管疾病風險的性別差異相對較小。本研究的目的在分析男女性第二型糖尿病人之照護連續性、用藥遵從度，以及主照顧醫師的年齡、性別、與專科別分佈的差異；並評估此分佈之性別差異對於第二型糖尿病人冠狀動脈疾病與中風相對危險性性別差異相對較小的解釋能力。
方法：本計畫利用2000年健保百萬人承保抽樣歸人檔進行2個世代研究。第一個世代研究用以探討照護連續性與用藥遵從度對解釋冠狀動脈疾病發生風險性別差異縮小的影響，樣本包括2000年12,715名(男女分別為6,316與6,399人)第二型糖尿病人以及經性別、年齡匹配的50,860非糖尿病對照組個案(男女分別為25,264與25,596人)。測量照護連續性與用藥遵從度的基線時間為2000年首次糖尿病診斷日期後的一年期間，結果變項是冠狀動脈住院事件，追蹤開時間是基線時間結束隔日，追蹤截止時間則是結果變項出現，退出健保、或是2013年12月31日，此分析考量樣本人口學變項與居住地區之地理區位與都市化程度的潛在干擾作用。第二個世代研究比較分析男女性糖尿病人主要照顧醫師之年齡、性別、與專科別，並探討這些醫師的特性在影響男女性糖尿病人中風發生風險性別差異縮小現象中所扮演的角色。此部分包括10,105名第二型糖尿病人(男女分別為4,962與5,143人)與39,804名對照組(男女分別為19,569與20235人)，主要照顧醫師的界定為2000年第一次第二型糖尿病診斷出現後3年期間(基線時間)一名糖尿病病人就醫紀錄中最常出現提供醫療照護的醫師，考慮的潛在干擾因素包括：病人社經人口學變項、糖尿病併發症嚴重分數指數、高血壓與肥胖等共病、以及糖尿病人之照護連續性與用藥遵從度，此部分分析的結果變項是中風住院事件，追蹤開時間是基線時間結束隔日，追蹤截止時間則是結果變項出現，退出健保、或是2013年12月31日。本研究兩部分的分析均使用Cox迴歸模式，計算相對風險及其95%信賴區間。
結果：第一部分：經過14年的追蹤，男、女性糖尿病人發生冠狀動脈住院的人數分別為1,251與1,227人，發生率為25.96/1,000人年與25.05/1,000人年，校正後的相對風險是1.11(95% CI=1.03-1.20)，此數值低於對照組男性之相對風險(Hazard Ratio=1.42, 95% CI=1.32-1.49)。在增加了控制了照護連續性與用藥遵從度後，相對風險修正為0.96(95% CI=0.91-1.01)。第二部分：經過14年的追蹤，男、女性糖尿病人發生中風的人數分別為1,202與1,204人，發生率為29.60/1,000人年與27.69/1,000人年，校正後的相對風險是1.248 (95% CI=1.146-1.360)，此數值略低於對照組男性之相

中文關鍵詞：二型糖尿病、照護連續性、藥物遵從度、健康照護工作者、族群世代研究

英文摘要：Aims: This study aims to analyze whether continuity of care, adherence to medication (indicated by medication possession ratio), and primary physician's age / sex/ specialty differ between male and female patients with type 2 diabetes; and to explore whether the above-mentioned factors could explain the reduced sex-difference in cardiovascular disease among patients with type 2 diabetes

mellitus.
Methods: The first cohort study, aiming to assess continuity of care and adherence to medication in explaining the reduced sex-difference in coronary heart disease, included 12,715 type 2 diabetes (men: 6,316; women: 6,399) with type 2 diabetes diagnosis in 2000, and 50,860 sex-age matched controls (men: 25,264; women: 25,596) Both continuity of care and adherence to medication was determined using the information of ambulatory care for type 2 diabetes and frequency of prescription identified from the 1-year period beginning from the earliest date of diagnosis of type 2 diabetes in 2000 (i.e., baseline period). The follow-up began from the first day after the 1-year baseline period. The date of end-of-follow-up was date of outcome incidence (i.e., coronary artery disease), date of health insurance termination, or the last day of 2013. Covariates considered in this part of analysis included demographics, administrative location of residence, and level of urbanization of residential area. The second cohort study included 10,105 type 2 diabetes subjects (men: 4,962; female: 5,143); control groups, on the other hand, included 39,804 (men: 19,569; women: 20,235) subjects. We used a 3-year period to identify the primary physician who provided the most frequent ambulatory care for the study subjects. In addition to socio-demographic characteristics, we also control for diabetes complication severity index (DCSIs), hypertension, obesity, continuity of care, and drug adherence. We performed Cox regression analysis to estimate hazard ratio (HR) of the above-mentioned two cardiovascular endpoints, and the corresponding 95% confidence intervals (CI)).
Results: 1st part: Over a 14-year period of follow-up, 1,252 male patients and 1,227 female patients with type 2 diabetes encountered admission for coronary artery disease, with an incidence density of 25.96/1,000 person-years and 25.05/1,000 person-years, respectively. It represented a covariate-adjusted hazard ratio of 1.11(95% CI=1.03-1.20), which was lower than that was observed for the control (i.e., non-diabetes) group (HR=1.42, 95% CI=1.32-1.49). After further adjustment for continuity of care and adherence to medication, the HR changed to 0.96 (95% CI=0.91-1.01). 2nd part: Over a 14-year period of follow-up, 1,202 male patients and 1,204 female patients with type 2 diabetes encountered admission for stroke, with an incidence density of 29,60/1,000 person-years and 27.69/1,000 person-years, respectively. The covariate-adjusted HR was estimated at 1.248 (95% CI=1.146-1.360), which was again slightly lower than that was observed for

the control (i.e., non-diabetes) group (HR=1.287, 95% CI=1.217-1.361). Further adjustment for primary physician’s age, sex, and specialty, the adjusted HR changed into 1.250 (95% CI=1.147-1.262).
Conclusions: Our cohort studies did not support the notation that continuity of care, adherence to medications, physician’s age / sex / specialty posed little influence on the reduced sex-differences in relative risk of cardiovascular disease in patients with type 2 diabetes.

英文關鍵詞： type 2 diabetes, cardiovascular disease, continuity of care, adherence to medication, healthcare workers, population-based cohort study

中文摘要

主旨：男性族群在心血管疾病的發生風險上明顯高於女性族群，不過，在糖尿病族群中，男女性發生心血管疾病風險的性別差異相對較小。本研究的目的在分析男女性第二型糖尿病人之照護連續性、用藥遵從度，以及主照顧醫師的年齡、性別、與專科別分佈的差異；並評估此分佈之性別差異對於第二型糖尿病人冠狀動脈疾病與中風相對危險性性別差異相對較小的解釋能力。

方法：本計畫利用 2000 年健保百萬人承保抽樣歸人檔進行 2 個世代研究。*第一個世代研究*用以探討照護連續性與用藥遵從度對解釋冠狀動脈疾病發生風險性別差異縮小的影響，樣本包括 2000 年 12,715 名(男女分別為 6,316 與 6,399 人)第二型糖尿病人以及經性別、年齡匹配的 50,860 非糖尿病對照組個案(男女分別為 25,264 與 25,596 人)。測量照護連續性與用藥遵從度的基線時間為 2000 年首次糖尿病診斷日期後的一年期間，結果變項是冠狀動脈住院事件，追蹤開時間是基線時間結束隔日，追蹤截止時間則是結果變項出現，退出健保、或是 2013 年 12 月 31 日，此分析考量樣本人口學變項與居住地區之地理區位與都市化程度的潛在干擾作用。第二個世代研究比較分析男女性糖尿病人主要照顧醫師之年齡、性別、與專科別，並探討這些醫師的特性在影響男女性糖尿病人中風發生風險性別差異縮小現象中所扮演的角色。此部分包括 10,105 名第二型糖尿病人(男女分別為 4,962 與 5,143 人)與 39,804 名對照組(男女分別為 19,569 與 20235 人)，主要照顧醫師的界定為 2000 年第一次第二型糖尿病診斷出現後 3 年期間(基線時間)一名糖尿病病人就醫紀錄中最常出現提供醫療照護的醫師，考慮的潛在干擾因素包括：病人社經人口學變項、糖尿病併發症嚴重分數指數、高血壓與肥胖等共病、以及糖尿病人之照護連續性與用藥遵從度，此部分分析的結果變項是中風住院事件，追蹤開時間是基線時間結束隔日，追蹤截止時間則是結果變項出現，退出健保、或是 2013 年 12 月 31 日。本研究兩部分的分析均使用 Cox 迴歸模式，計算相對風險及其 95%信賴區間。

結果：第一部分：經過 14 年的追蹤，男、女性糖尿病人發生冠狀動脈住院的人數分別為 1,251 與 1,227 人，發生率為 25.96/1,000 人年與 25.05/1,000 人年，校正後的相對風險是 1.11(95% CI=1.03-1.20)，此數值低於對照組男性之相對風險(Hazard Ratio=1.42, 95% CI=1.32-1.49)。在增加了控制了照護連續性與用藥遵從度後，相對風險修正為 0.96(95% CI=0.91-1.01)。第二部分：經過 14 年的追蹤，男、女性糖尿病人發生中風的人數分別為 1,202 與 1,204 人，發生率為 29.60/1,000 人年與 27.69/1,000 人年，校正後的相對風險是 1.248 (95% CI=1.146-1.360)，此數值略低於對照組男性之相對風險(Hazard Ratio=1.287, 95% CI=1.217-1.361)。在增加了控制了主要照顧醫師的年齡、性別、與專科別後，相對風險修正為 1.250 (95% CI=1.147-1.262)。

結論：本研究的數據並未發現照護連續性、用藥遵從度、以及醫師年齡、性別、與專科別並不能解釋第二型糖尿病族群心血管疾病發生率性別差異縮小的現象。

關鍵詞: 第二型糖尿病、照護連續性、藥物遵從度、健康照護工作者、族群世代研究

Abstract

Aims: In the general population, men have higher cardiovascular disease than women. However, the sex-difference in cardiovascular disease risk was reduced in the population with type 2 diabetes. This study aims to analyze whether continuity of care, adherence to medication (indicated by medication possession ratio), and primary physician's age / sex/ specialty differ between male and female patients with type 2 diabetes; and to explore whether the above-mentioned factors could explain the reduced sex-difference in cardiovascular disease among patients with type 2 diabetes mellitus.

Methods: Data analyzed in the 2 cohort studies included in this study were medical claims of 1-million beneficiaries retrieved from Taiwan's National Health Insurance Dataset. The first cohort study, aiming to assess continuity of care and adherence to medication in explaining the reduced sex-difference in coronary heart disease, included 12,715 type 2 diabetes (men: 6,316; women: 6,399) with type 2 diabetes diagnosis in 2000, and 50,860 sex-age matched controls (men: 25,264; women: 25,596) Both continuity of care and adherence to medication was determined using the information of ambulatory care for type 2 diabetes and frequency of prescription identified from the 1-year period beginning from the earliest date of diagnosis of type 2 diabetes in 2000 (i.e., baseline period). The follow-up began from the first day after the 1-year baseline period. The date of end-of-follow-up was date of outcome incidence (i.e., coronary artery disease), date of health insurance termination, or the last day of 2013. Covariates considered in this part of analysis included demographics, administrative location of residence, and level of urbanization of residential area. The second cohort study assess the similarity of physician's age, sex, and specialty between male and female patients with type 2 diabetes, and role of these physicians' characteristics in explaining the reduced sex-difference in stroke. Type 2 diabetes group included 10,105 subjects (men: 4,962; female: 5,143); control groups, on the other hand, included 39,804 (men: 19,569; women: 20,235) subjects. We used a 3-year period to identify the primary physician who provided the most frequent ambulatory care for the study subjects. In addition to socio-demographic characteristics, we also control for diabetes complication severity index (DCSIs), hypertension, obesity, continuity of care, and drug adherence. The follow-up began from the first day after the 3-year baseline period. The date of end-of-follow-up was date of outcome incidence (i.e., stroke), date of health insurance termination, or the last day of 2013. We performed Cox regression analysis to estimate hazard ratio (HR) of the above-mentioned two cardiovascular endpoints, and the corresponding 95% confidence intervals (CI)).

Results: 1st part: Over a 14-year period of follow-up, 1,252 male patients and 1,227 female patients with type 2 diabetes encountered admission for coronary artery disease, with an incidence density of 25.96/1,000 person-years and 25.05/1,000 person-years, respectively. It represented a covariate-adjusted hazard ratio of 1.11(95% CI=1.03-1.20), which was lower than that was observed for the control (i.e., non-diabetes) group (HR=1.42, 95% CI=1.32-1.49). After further adjustment for continuity of care and adherence to medication, the HR changed to 0.96 (95% CI=0.91-1.01). 2nd part: Over a 14-year period of follow-up, 1,202 male patients and 1,204 female patients with type 2 diabetes encountered admission for stroke, with an incidence density of 29,60/1,000 person-years and 27.69/1,000 person-years, respectively. The covariate-adjusted HR was estimated at 1.248 (95% CI=1.146-1.360）, which was again slightly lower than that was observed for the control (i.e., non-diabetes) group (HR=1.287, 95% CI=1.217-1.361). Further adjustment for primary physician's age, sex, and specialty, the adjusted HR changed into 1.250 (95% CI=1.147-1.262).

Conclusions: Our cohort studies did not support the notation that continuity of care, adherence to medications, physician's age / sex / specialty posed little influence on the reduced sex-differences in relative risk of cardiovascular disease in patients with type 2 diabetes.

Keywords: type 2 diabetes, cardiovascular disease, continuity of care, adherence to medication, healthcare workers, population-based cohort study

1. Introduction

Diabetes is a curse of modern life, with an estimated global prevalence of over 350 million (Whiting et al., 2011). Across the world it is on the rise, with a projected increase to 438 million by 2030 with most of the burden occurring in lower- and middle-income countries (Whiting et al., 2011). Diabetes confers increased risk of microvascular and macrovascular events in both men and women (Kannel and McGee, 1979). However, women with type 2 diabetes have been reported to have significantly higher risks of both fatal and non-fatal coronary heart disease (CHD) and stroke than men with diabetes (Peters et al., 2014a; Peters et al., 2014b; Huxley et al., 2015). Peters et al. (2014) conducted a meta-analysis that investigated prospective relationships between diabetes and incident CHD in men and women, reporting that women with diabetes have more than a 40% greater risk for developing CHD than men with diabetes. Another meta-analysis that investigated prospective relationships between diabetes and incident stroke in men and women, reporting that women with diabetes have a significantly higher risk of incident stroke than men with diabetes. They report these findings independent of sex differences in other major cardiovascular risk factors (Peters et al., 2014b; Maric-Bilkan, 2017).

Interestingly, in the absence of diabetes, women have a far lower risk of macro-vascular disease compared with men for much of their lifespan. Thus, the presence of diabetes confers greater risk for vascular complications in women compared with men and some of the potential reasons, including contribution of sex hormones and sex-specific risk factors are proposed. There is a growing body of evidence that sex hormones play an important role in the regulation of cardiovascular function. While estrogens are generally considered to be cardioprotective and androgens detrimental to cardiovascular health, recent findings challenge these assumptions and demonstrate diversity and complexity of sex hormone action on target tissues, especially in the setting of diabetes (Kim et al., 2015; Ding et al., 2006). Other potential mechanisms also include the increased likelihood that cardiovascular disease (CVD) risk factors are more strongly associated with diabetes in women than in men, and sex differences in the effectiveness of pharmacologic therapies and the prescription of such therapies (Lyon et al., 2015).

Women could do worse when they develop diabetes because they do not have the same access to appropriate, cardio-protective, health care as do men who develop diabetes. There is a great wealth of evidence to show that women have, in the past, received poorer cardiovascular care than men – although campaigns such as 'Go Red for Women' (www.goredforwomen.org) have prompted a great improvement, at least in industrialized nations. Some previous studies reported in adequate accessibility to optimal diabetes care for women patients. For example, the 2012–2013 report from the UK National Diabetes Audit (Health and Social Care Information Centre, 2014), including about 2 million individuals with diabetes, found that women were 15% less likely than men to receive the care recommended by the national guidelines or to meet treatment targets. Additionally, data from a US study of more than 147,000 outpatients with established heart disease, conducted 2010–2012, reported that women were 37% less likely to be prescribed antiplatelet medication compared with men and, in individuals with diabetes, women were 25% less likely to achieve target cholesterol levels than men (Eapen et al., 2014).

Recent data from a very large study in the USA and its territories (Kirkman et al., 2015) found adherence to antidiabetic medication to be slightly lower among women. Moreover, It is also likely that physicians have undoubtedly been liable to treat CVD as predominantly a 'man's disease' in the past, and perhaps some physicians still think this way, even if not consciously so (Woodward et al., 2015). To further explore the potential roles of patients' compliance to diabetes care, and physicians' characteristics (mainly age and sex) in the explanation of sex differences, in diabetes, relating to health care accessibility.

2. Materials and methods

2.1 Data source

The study proposal was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EX-106-006). Data were retrieved from Taiwan's NHI research database, a medical claim database that stores the medical records of beneficiaries that are uploaded by medical institutions to obtain reimbursement from NHI. Taiwan's NHI program universally covers medical insurance for nearly all (> 97%) Taiwanese citizens (prisoners and military personnel were exempted in our study period) (National Health Insurance Administration, 2005). The National Health Insurance Administration performs quarterly expert reviews on a random sample of medical claims to ensure their accuracy (Cheng, 2003).

The NHIRD provides encrypted patient identification number (PIN), gender, birthday, dates of admission (ambulatory care visit), date of discharge (for inpatient claim), medical institutions providing health services, *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) diagnosis (up to five) and procedure (up to five) codes, outcome at hospital discharge (recovered, died, or transferred), and co-payments charged to patients. Medical orders including drugs prescribed were also included. Information on medical personnel (including physicians and other health care workers), including licensed date, specialization, employment area, employment type, and encrypted identification number, which can be linked to claims data, is also available.

With ethical approval from the Review Committee of National Health Research Institutes, we used claim data (1997-2013) from one million people randomly selected from the NHIRD in 2000. The complete dataset of medical claims can be inter-linked through each individual's PIN.

2.2 Research design and study cohorts

2.2.1 Adherence and continuity of care in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes

This was a claim data-based cohort study. The type 2 diabetes group included all patients who sought ambulatory care type 2 diabetes (International Classification of Disease, 9th revision, Clinical Modification ICD-9-CM: 250.×0 or 250.×2) in 2000 and had ≥ 2 ambulatory care visits for within a 365-day period following the first ambulatory visit in 2000 (i.e., diagnosis date). Patients in the type 2 diabetes group must be older than 18 years at diagnosis date, without a history of CVD (including coronary artery disease (CAD) (ICD-9-CM: 410-414 and 428; A-code: A291, A292, A293, A299), cerebral vascular at-tack (ICD-9-CM: 430–436), and coronary revascularization procedures（ICD-9-CM: 36.0, 36.01, 36.02, 36.05, 36.06, 36.1, 36.10–36.19)) between 1997/01/01 and diagnosis date+365 days, encounter termination of his/her NHI policy within 1-year period after diagnosis date, and free from diagnoses of type 1 diabetes (ICD-9-CM: 250.×1 or 250.×3) between 1997/01/01 and diagnosis date+365 days. A total of 12,715 patients with type 2 diabetes eligible for analysis were identified; the patients could include both prevalent type 2 diabetes patients diagnosed prior to 2000, and those type 2 diabetes newly diagnosed in 2000.

The potential control subjects were people who did not have any ambulatory diagnosis of type 1 or type 2 diabetes prior to 2001/12/31. Exclusion was also made for those who had a CVD history between 1997/01/01 and 2001/12/31 or withdrew from the NHI program prior to 2001/12/31. Selection of controls was made by individually matching each type 2 diabetes on age and sex with a case/control ratio of 1/4. Date of the first appearance of type 2 diabetes in medical claims of each patient with type 2 diabetes and his/her matched control was considered as the date of enrollment. Flow chart of the study subjects' enrollment is illustrated in Figure 1.

2.2.2 Physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes

Similar to the first part of the study, the second part of study was also a claim data-based cohort study, that investigated physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes. The type 2 diabetes group included all patients who sought ambulatory care type 2 diabetes (International Classification of Disease, 9th revision, Clinical Modification ICD-9-CM: 250.×0 or 250.×2) in 2000 and had ≥ 2 ambulatory care visits for within a 365-day period following the first ambulatory visit in 2000 (i.e., diagnosis date). Patients in the type 2 diabetes group must be older than 18 years at diagnosis date, without a history of CVD (including coronary artery disease (CAD) (ICD-9-CM: 410-414 and 428; A-code: A291, A292, A293, A299), cerebral vascular at-tack (ICD-9-CM: 430–436), and coronary revascularization procedures（ICD-9-CM: 36.0, 36.01, 36.02, 36.05, 36.06, 36.1, 36.10–36.19)) between 1997/01/01 and diagnosis date+3 years, encounter termination of his/her NHI policy within 3-year period after diagnosis date, and free from diagnoses of type 1 diabetes (ICD-9-CM: 250.×1 or 250.×3) between 1997/01/01 and diagnosis date+3 years. We further excluded those type 2 diabetes patients whose primary physician's information on sex and age was missing. A total of 10,105 patients with type 2 diabetes eligible for analysis were identified; the patients could include both prevalent type 2 diabetes patients diagnosed prior to 2000, and those type 2 diabetes newly diagnosed in 2000.

The potential control subjects were people who did not have any ambulatory diagnosis of type 1 or type 2 diabetes prior to 2001/12/31. Exclusion was also made for those who had a CVD history between 1997/01/01 and 2003/12/31 or withdrew from the NHI program prior to 2003/12/31. Selection of controls was made by individually matching each type 2 diabetes on age and sex with a case/control ratio of 1/4. Date of the first appearance of type 2 diabetes in medical claims of each patient with type 2 diabetes and his/her matched control was considered as the date of enrollment. Flow chart of the study subjects' enrollment is illustrated in Figure 2.

2.3 Measurements of exposure

In the analysis of patient's adherence to anti-diabetic drugs and treatment in association with treatment outcome, we used a 1-year period, starting from date of first presence of type 2 diabetes diagnosis codes in 2000 (i.e., diagnosis date) to the day of diagnosis date + 365 days, as the baseline. On the other hand, in the analysis of physicians' characteristics in relation to treatment outcome, we alternatively used a 3-year period (the day of type 2 diabetes diagnosis date + 1,095 days) as the baseline period in order to obtain more ambulatory care visit information, which may better be used to determine the primary physician who provided diabetes care for each patient.

2.3.1 Medication possession ratio (MPR)

Adherence to anti-diabetic drugs was evaluated on the basis of the refill pattern during the first year after type 2 diabetes diagnosis (i.e., baseline period). The number of prescription-days were estimated from the quantity of drugs from pharmacy claims in the NHIRD. Refill adherence was defined as the medication possession ratio (MPR) at baseline period, computed by dividing the total number of prescription days the patient received by 365 days or 1095 days. For example, if the amount of anti-diabetic drug prescriptions a patient received covered a total of 9 months during a 1-year period, the patient would be considered 75% adherence. If the calculated MPR for a patient was >100%, the MPR was considered 100%. Most compliance studies considered an MPR ≥80% as good compliance (Siris et al, 2006; Rabenda et al., 2008); therefore, this cutoff point was adopted in our study.

2.3.2 Continuity of care

Continuity of care (COC) score was calculated based on outpatient services only. Considering the variation and very high number of physician visits in Taiwan, we chose the continuity of care index (COCI) as our predictor variable because the COCI is minimally sensitive to the number of physician visits by patients (Smedby et al., 1986). The COCI was composed of the number of different physicians seen and the number of visits to each physician. The COCI value ranges between 0 and 1, with a higher value representing better COC. The equation for the COCI was as follows:

$$\mathrm{COCI} = \frac{\sum_{j=1}^{M} n_j^2 - N}{N(N-1)}$$

N represents the total number of physician visits, nj is the number of visits to the same physician (j), j is a given physician, and M is the number of physicians. In a study by Bice and Boxerman (1977) (Bice and Boxerman, 1977), the summation term in the numerator was the sum of the number of unreferred physicians. Because of the lack of referral arrangements in Taiwan, we used the total number of physician visits in the analysis. Also, because the COCI values have no inherent clinical meaning, we categorized them into two categories, namely <80% and >=80%, according to the distribution of scores across the entire study population at baseline. For the first and second part of the study, the COCI score was calculated based on a 365-day and 1,095-day period, respectively, after date of the first type 2 diabetes diagnosis in 2000.

2.3.3 The primary physician who provided diabetes care

The primary physician who provided diabetes care for the patients with type 2 diabetes was determined according to the frequency of ambulatory care visits made by each of the diabetes patients. The physician who provided the largest number of ambulatory care for specific diabetes patient within the 3-year period after the first type 2 diabetes diagnosis was present in 2000. If more than one physician made the same number of ambulatory care visits, the physician who cared the patient at the earliest time was selected to be the primary physician. The age of physician was calculated at the time of first ambulatory care provided.

2.4 Follow-up and outcome ascertainment

2.4.1 Adherence and continuity of care in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes

In the first part of study that investigated the MPR / COCI in relation to treatment outcome, we defined the starting date of follow-up (i.e., index date) as the type 2 diabetes diagnosis date + 365 days. We then linked study subjects, using the unique person identification number (PIN), to inpatient claims (2001-2013) in an attempt to identify the possible admissions with the primary or secondary diagnoses with codes of coronary artery disease and revascularization procedures (acute myocardial infarction (ICD-9-CM: 410), ischemic heart disease (ICD-9-CM: 410–414), coronary revascularization procedures (ICD-9-CM: 36.0, 36.01, 36.02, 36.05, 36.06, 36.1, 36.10–36.19).

2.4.2 Physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes

In the analysis of physicians' characteristics in relation to treatment outcome, we defined the starting date of follow-up (i.e., index date) as the type 2 diabetes diagnosis date + 1,095 days. With the unique PIN, we were able to link both diabetes and comparison groups to the inpatient claims (2003– 2013) to identify the first episode of primary or secondary diagnosis of non-traumatic hemorrhagic stoke (ICD-9-CM: 430– 432) and ischemic stroke (ICD-9-CM: 433–438) as the end points of this study.

A validation study reviewed the NHI claims data of 1,736 consecutive acute ischemic stroke (AIS) patients, of whom 1,299 (74.8%) were linked successfully to the stroke registry database. It shows that the PPV was 88.4% (95% CI, 86.8%-89.8%) and sensitivity was 97.3% (95% CI, 96.4%-98.1%) (Hsieh et al., 2015).

2.5 Measurements of covariates

2.5.1 Adherence and continuity of care in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes

Sociodemographic characteristics, including age, sex, city/township of residence, and personal income-based insurance premium were abstracted from the NHI beneficiary registration. Age was determined on the index date. Level of urbanization for each of the 368 cities/townships in Taiwan was determined by the method by Liu et al. who classified all cities and townships of Taiwan into seven ordered levels of urbanization according to various indicators, including population density, proportion of residents with college or higher education, percentage of elderly (>65 years) people, proportion of the agricultural workforce, and number of physicians per 10^5 people (Liu et al., 2006). We employed the median family annual income of each city/township to indicate the neighborhood socioeconomic status for each study subject. Consideration of urbanization level and neighborhood socioeconomic status was made to account for differential diagnostic techniques in different areas; and for varying health care accessibility (Tan et al., 2005).

2.5.2 Physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes

In addition to the socio-demographic covariates mentioned in the preceding paragraph, selected co-morbidity, including hypertension and obesity, and Diabetes Complication Severity Index (DCSI) were also considered as covariates in this part of analysis. DCSI was calculated from diabetic complications, including retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular, and metabolic disorders (Chang et al., 2012; Young et al., 2008). The DCSI was reportedly has a favorable correlation with diabetes duration (Young et al., 2008).

Each predefined diabetic complication was identified according to the relevant ICD-9CM codes presented in medical records within 1 year or at least one inpatient record between 1 January 1997 (or entry of NHI) and index date. Similar rules were also applied in identifying histories of hypertension (ICD-9-CM: 401, 402, and 405; A-code: A269) and obesity (ICD-9-CM: 278).

2.5 Statistical analysis

Similar analytical strategies were employed in the two parts of analyses. The distributions of covariates were compared between the 4 study groups, according to patient's age and sex. The exposure variables (i.e., COCI, MPR, physicians' characteristics) were analyzed only for patients with type2 diabetes. We first examined the overall and sex- and age-specific association of type 2 diabetes with risk of coronary artery disease and stroke. Crude and covariate adjusted hazard ratios (HRs) were estimated from Cox proportional hazard model. The covariates mentioned above with or without severe hypoglycaemia were simultaneously adjusted in multivariable Cox models.

The data were analyzed using SAS (version 9.4; SAS Institute, Cary, NC). A *p*-value of 0.05 or less was considered statistically significant.

3. Results

3-1. Adherence and continuity of care in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes

A total of 12,715 patients with type 2 diabetes (6,316 men and 6,399 women) and 50,860 controls (25,264 men and 25,596 women) were identified. The mean age for diabetes men and women was 58.79 and 60.98 years, respectively. Similar figures were noted for controls. Distributions of residential area were similar between men and women, as well as between diabetes and non-diabetes groups. Most study subjects were from northern Taiwan, and living in cities/townships with higher level of urbanization (Table 1). Among type 2 diabetes patients, women had a higher rate of adherence to anti-diabetic medications with a mean±standard deviation (SD) medication possession ratio (MPR) of 73.07%±28.69%, as compared to 69.82%± 29.22% in men. The proportion of MPR >= 80% for diabetes men and women was 50.7% and 44.9%, respectively. Women patients also had somewhat higher mean continuity of care (COC) versus men (64.13%± 30.34% vs 62.17%± 31.47%) (Table 1).

Table 2 shows the sex-specific incidence density and relative hazard of CAD and revascularization procedures. Among the non-diabetes, men had a significantly higher risk of CAD and revascularization procedures (8.67 vs 6.88 per 1,000 person-tears), with a covariate adjusted hazard ratio (HR) of 1.42 (95% CI, 1.32-1.49). The risks of CAD and revascularization procedures substantially increased for both men and women in patients with type 2 diabetes; however, the sex difference in relative hazard significantly diminished to 1.11 (95% CI, 1.03-1.20) (*p*-value for interaction=0.0002). When adjustment was further performed by including MPR and COCI, the relative hazard further reduced and became insignificant (HR=0.96, 95% CI, 0.91-1.01) (Table 2).

3-2. Physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes

Similar numbers of men (n=4,962) and women (n=5,143) were observed in 10,105 people with type 2 diabetes. There were 19,569 men and 20,235 women in 39,804 controls (i.e., non-diabetes). Men were slightly younger than women in both type 2 diabetes and controls. In addition, men had higher income levels than women in both groups. Moreover, the living districts for men and women were similar with respect to geographic area and urbanization level. Among type 2 diabetes, the DCSI scores were similar between men and women with type 2 diabetes. The prevalence of both hypertension (54.21% vs 48.35%) and obesity (1.4% vs 0.81%) was higher in women than in women and obesity (Table 1).

Women type 2 diabetes tended to have higher averaged medication possession ratio (MPR, 72.23 ±27.91 vs 68.17 ±29.32), and continuity of care (COC, 0.5672±0.2862 vs 0.5559±0.2963). With respect to the physicians' characteristics, men and women type 2 diabetes were treated by physicians of similar gender, age, and specialties (Table 1).

Table 4 shows HRs of stroke in relation to patient's sex, according to diabetes status. Male gender was associated with a significantly increased HR (1.287, 95%, 1.217-1.361) among non-diabetes after adjustment for patient's socio-demographics, DCSI, and selected co-morbidity. The covariate adjusted HR slightly reduced to 1.248 for study subjects among type 2 diabetes (HR=1.248, 95% CI, 1.146-1.360). The adjusted HR remained unchanged (HR=1.250, 95% CI, 1.147-1.362) when further adjustment was made for physicians' gender, age, and specialities.

4. Discussion

Women have a lower risk of CVD than men, but the difference, in relative terms is less when they, and their male comparator, have diabetes. Nevertheless, the 'catching up' process after diabetes is scientifically intriguing and worthy of serious research. Women and men are of the same species and largely subject to the same environmental exposures but are, intrinsically, biologically different. Hence, it is reasonable to propose that some of the 'catching-up' in vascular risk by women after they develop diabetes is due to inherent physiological, hormonal or genetic differences (Woodward et al., 2015). Very few studies were ever conducted to assess whether there are non-biological causes that could explain such 'catching-up' effect. The accessibility explanation is among those potential non-biological causes. Women could do worse when they develop diabetes because they do not have the same access to appropriate, cardio-protective, health care as do men who develop diabetes. There is a great wealth of evidence to show that women have, in the past, received poorer cardiovascular care than men (Woodward et al., 2015). In this study, we attempted to assess whether the continuity of care and adherence to medications are responsible for the reduced relative risk of cardiovascular disease associated with gender. Our study results did not support the notation that women patients with type 2 diabetes had lower continuity of care or poor adherence to medication than their male counterparts.

It is debatable whether this sex inequality is due to women underestimating, or ignoring, their risk, relative to men, or whether it is due to structural biases in cardiovascular health provision. However, it seems unlikely that women will, in general, be less aware of the adverse consequences of unhealthy risk behaviors, relative to men (Green et al., 2003). Nevertheless, data from a very large study in the USA and its territories (Kirkman et al., 2015) found adherence to anti-diabetic medication to be slightly lower among women. Possibly women have a different concept of personal risk to men, at least in terms of its importance for them relative to other members of their immediate family. Shrestha et al. (2013) conducted a cross-sectional survey of 100 men and 100 women with type 2 diabetes in Western Nepal to study the gender differences in the social structure that could bring differences in lifestyle modifications and all other self-care behaviors in type 2 diabetes. It showed that dry mouth and abdominal pain were reported as symptoms of diabetes in 51% and 31% women compared to 37% and 19% men respectively. The study also revealed that women had low self-efficacy with respect to their diabetes care (35%) in comparison to men (65%). There was significant association between gender and diet practices which showed men have 0.328 (95% CI: 0.184 - 0.585) times less chances of bad dietary practices compared to women. After adjusting for age, education, occupation and self-efficacy, men were less likely to have bad dietary practices (OR= 0.513, 95% CI: 0.266, 0.992).

Apart from patients' side, a number of studies were conducted to investigate physicians' characteristics in explain the sex differences in various health outcomes. These characteristics include a physician's age (Tsugawa et al., 2018; Tsugawa et al., 2017b; Waljee et al., 2006), sex (Tsugawa et al., 2018; Tsugawa et al., 2018; Tsugawa et al., 2017a; Wallis et al., 2017), and specialty (Archampong et al., 2012; Sahni et al., 2016). Physicians have undoubtedly been liable to treat CVD as predominantly a 'man's disease' in the past, and perhaps some doctors still think this way, even if not consciously so. But any explanation of sex differences, in diabetes, relating to access has to consider why no sex difference is seen in hypertension (Peters et al., 2013), which is arguably the strongest risk factor for CVD. Our study did not disclose meaningful influence of physicians' age, sex, and specialty on the reduced relative risk of coronary artery disease or stroke in relation to gender.

This study could have incurred potential bias in the results. First, exclusive reliance on the claims data might have resulted in potential disease misclassification bias. The accuracy of a single diabetes diagnosis in the NHI claim data in 2000 was reported to be 74.6% (Lin et al., 2005), but we used at least two diagnoses of type 2 diabetes, with the first and the last visits >30 days apart, which may reduce the likelihood of disease misclassification. Despite that, the control group might still have included people with new-onset or undiagnosed diabetes. Such misclassification bias, however, was likely to be non-differential, which tends to underestimate rather than overestimate the true relative risks. Second, a number of potential confounders including body mass index, disease duration, physical activities, smoking and alcohol consumption were not considered in our analysis, mainly because of the unavailability of these data. Inadequate adjustment for potential confounders might have resulted in residual confounding. Third, our exclusive reliance on inpatient claims for the coronary artery disease and stroke would have missed some of the patients who were not hospitalized, which could underestimate the incidence rate, but it would have had little influence on the relative risk estimates associated with type 2 diabetes. Fourth, we retrieved the information of prescriptions from claim data, but we are not aware whether the study patients truly consume the drugs. Lastly, data analyzed in this study were entirely from ethnic Chinese people; the findings may not therefore be generalizable to other ethnic populations.

In conclusion, our cohort studies did not support the notation that continuity of care and adherence to medications may explain the reduced sex-differences in relative risk of coronary artery disease and stroke in patients with type 2 diabetes. Additionally, physician's age and sex also posed little influence on he reduced sex-differences in relative risk of coronary artery disease and stroke in patients with type 2 diabetes.

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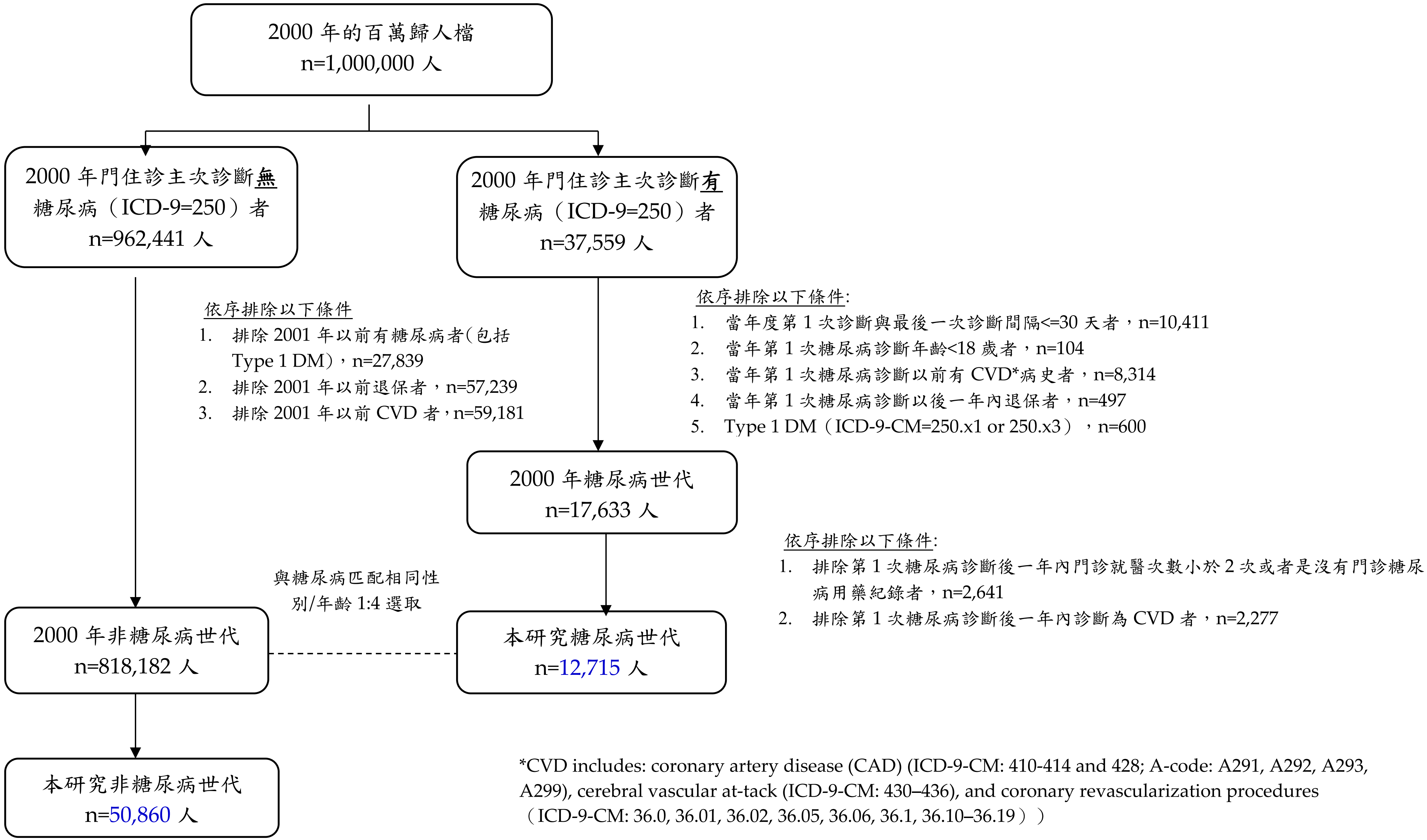

Figure 1. Flow chart of study subjects' enrollment for the analysis of *adherence and continuity of cares in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes.*

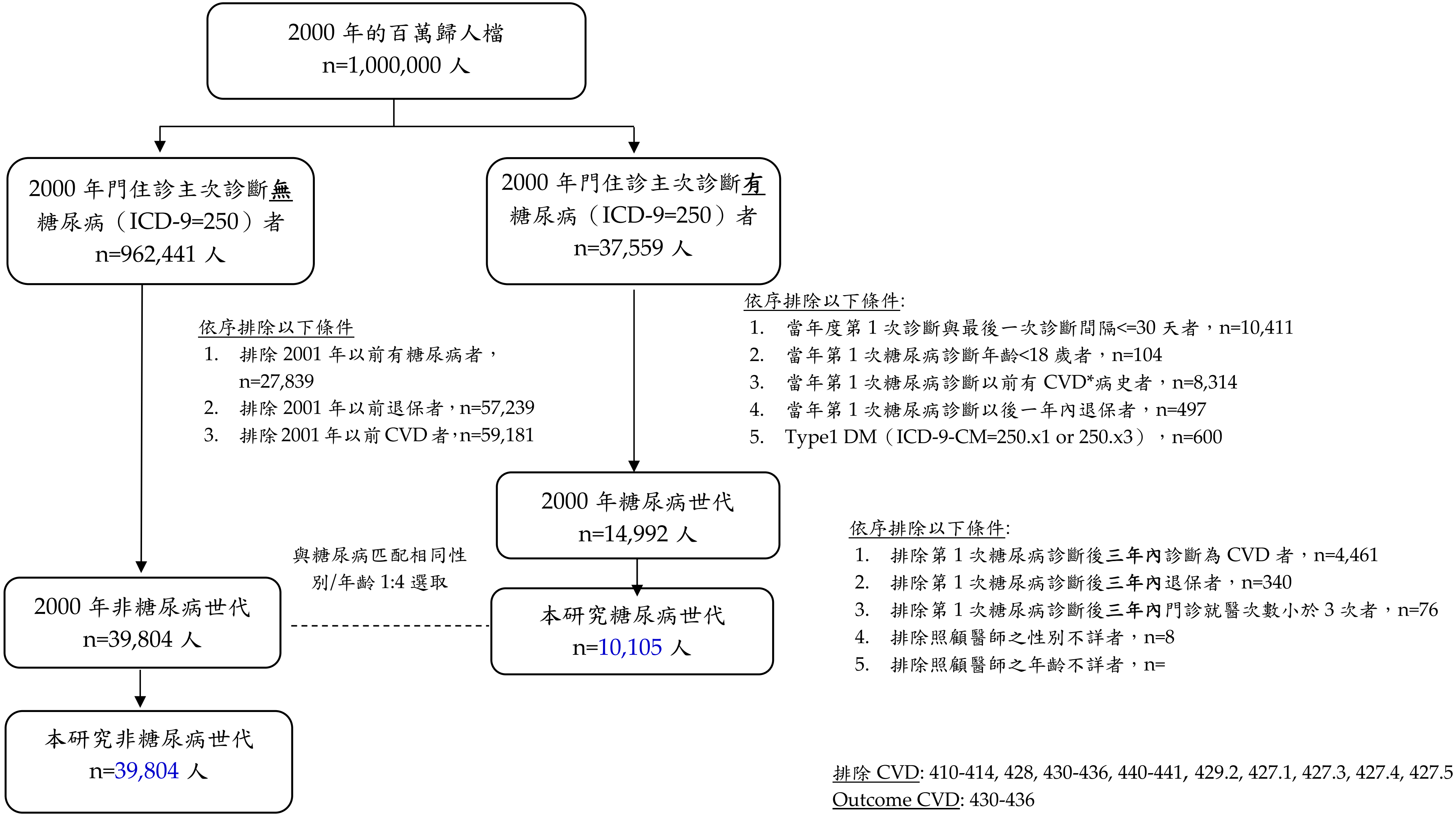

Figure 2. Flow chart of study subjects' enrollment for the analysis of *physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes*.

Table 1. The characteristics of study cohort for the analysis of *adherence and continuity of cares in the explanation of sex differences in coronary heart disease among patients with type 2 diabetes*

	Type 2 diabetes N=12,715		Non-Diabetes N=50,860	
	Male N=6,316 n(%)	Female N=6,399 n(%)	Male N=25,264 n(%)	Female N=25,596 n(%)
Age (yrs)				
18-44	762(12.1)	513(8.0)	3,048(12.1)	2,052(8.0)
45-64	3,364(53.3)	3,312(51.8)	13,456(53.3)	13,248(51.8)
65+	2,189(34.7)	2,574(40.2)	8,756(34.7)	10,296(40.2)
Mean±SD	58.79± 12.10	60.98± 11.40	58.79± 12.10	60.98± 11.39
Geographic area				
Northern	2,650(42.0)	2,770(43.3)	11,468(45.4)	11,559(45.2)
Central	1,454(23.0)	1,544(24.1)	5,809(23.0)	5,939(23.2)
Southern	2,000(31.7)	1,874(29.3)	7,177(28.4)	7,261(28.4)
Eastern	212(3.4)	211(3.3)	810(3.2)	837(3.3)
Urbanization status				
Urban area	2,755(43.6)	2,654(41.5)	10,674(42.3)	10,987(42.9)
Satellite area	1,665(26.4)	1,658(25.9)	6,897(27.3)	6,598(25.8)
Rural area	1,894(30.0)	2,087(32.6)	7,693(30.5)	8,011(31.3)
Medication possession ratio (MPR)				
<80%	3,481(55.1)	3,158(49.4)	-	-
>=80%	2,835(44.9)	3,241(50.7)	-	-
Mean±SD	69.82± 29.22	73.07± 28.69	-	-
Continuity of care (COC)				
<80%	3,885(61.5)	3,856(60.3)	-	-
>=80%	2,431(38.5)	2,543(39.7)	-	-
Mean±SD	62.17± 31.47	64.13± 30.34	-	-

*Inconsistency between total population and population summed for individual variable was due to missing information.

Table 2. Relative hazards of *coronary artery diseases* in relation to patient's sex, according to diabetes status

Characteristics	No. of people	Person-years followed	Coronary artery disease		Adjusted HR(95%CI)[a]	Adjusted HR(95%CI)[b]
			No. of cases	Incidence density, per 1000 person-years (95% CI)		
Non-Diabetes						
Gender						
Male	25264	248768.1	2180	8.76 (8.40-9.14)	1.42 (1.32-1.49)	
Female (Ref.)	25596	252451.9	1738	6.88 (6.54-7.22)	1.00	
Type 2 diabetes						
Gender						
Male	6316	48185.2	1251	25.96 (24.54-27.44)	1.11 (1.03-1.20)	0.96 (0.91-1.01)
Female (Ref.)	6399	48988.7	1227	25.05 (23.66-26.48)	1.00	1.00

*P value for the interaction between diabetes and gender is 0.0002.

[a] Based on Cox proportional hazard regression with adjustment for age, sex, geographic area and urbanization status, HR, hazard ratio; CI, confidence interval.

[b] Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, medication possession ratio, and continuity of care index.

Table 3. The characteristics of study cohort for the analysis of *physicians' characteristics in the explanation of sex differences in stroke among patients with type 2 diabetes.*

	Type 2 diabetes N=10,105		Non-Diabetes N=39,804	
	Male N=4,962 n(%)	Female N=5,143 n(%)	Male N=19,569 n(%)	Female N=20,235 n(%)
Age (yrs)				
18-44	586 (11.81)	393 (7.64)	2,344 (11.98)	1,594 (7.88)
45-64	2,778 (55.99)	2,704 (52.58)	10,994 (56.20)	10,580 (52.31)
65+	1,598 (32.20)	2,046 (39.78)	6,225 (31.82)	8,052 (39.81)
Mean±SD	58.97± 11.82	61.44± 11.29	58.86±12.10	61.35± 11.31
Income categories (NTD)				
0	812 (16.36)	1,885 (36.65)	2,985 (15.25)	7,095 (35.06)
<15,840	776 (15.64)	352 (6.84)	2,963 (15.14)	1,453 (7.18)
15,840-28,800	2,304 (46.43)	2,692 (52.34)	9,310 (47.58)	10,316 (50.98)
>28,800	1,070 (21.56)	214 (4.16)	4,311 (22.03)	1,371 (6.78)
Geographic area				
Northern	2,109 (42.50)	2,239 (43.53)	8,987 (45.92)	9,296 (45.94)
Central	1,102 (22.21)	1,199 (23.31)	4,568 (23.34)	4,720 (23.33)
Southern	1,588 (32.00)	1,544 (30.02)	5,412 (27.66)	5,610 (27.72)
Eastern	163 (3.28)	161 (3.13)	602 (3.08)	609 (3.01)
Urbanization status				
Urban area	2,147 (43.27)	2,128 (41.38)	8,281 (42.32)	8,559 (42.30)
Satellite area	1,329 (26.78)	1,353 (26.31)	5,391 (27.55)	5,429 (26.83)
Rural area	1,486 (29.95)	1,662 (32.30)	5,897 (30.13)	6,246 (30.87)
DCSI				
0	2,242 (45.18)	2,068 (40.21)	16,265 (83.12)	15,975 (78.95)
1	1,431 (28.84)	1,575 (30.63)	2,396 (12.24)	3,260 (16.11)
2	755 (15.22)	847 (16.47)	738 (3.77)	796 (3.93)
3	331 (6.67)	428 (8.32)	145 (0.74)	163 (0.81)
>=4	203 (4.09)	225 (4.37)	25 (0.13)	41 (0.20)
Median	1.00	1.00		
Hypertension				
Yes	2,399 (48.35)	2,788 (54.21)	3,702 (18.92)	5,080 (25.11)
No	2,563 (51.65)	2,355 (45.79)	15,867 (81.08)	15,155 (74.89)
Obesity				
Yes	40 (0.81))	72 (1.40)	33 (0.17)	88 (0.43)
No	4,922 (99.19)	5,071 (98.60)	19,536 (99.83)	20,147 (99.57)
Medication possession ratio (MPR)				
<80%	2,756 (55.54)	2,555 (49.68)	-	-
>=80%	2,206 (44.46)	2,588 (50.32)	-	-

Mean±SD	68.17 ±29.32	72.23 ±27.91	-	-
Continuity of care (COC)				
<0.8	3,529 (71.12)	3,677 (71.50)	-	-
>=0.8	1,433 (28.88)	1,466 (28.50)	-	-
Mean±SD	0.5559±0.2963	0.5672±0.2862	-	-
Physician's gender				
Male	4,497 (90.63)	4,648 (90.38)		
Female	465 (9.37)	495 (9.62)		
Physician's age (yrs)				
<35	202 (4.07)	191 (3.71)		
35-44	2,400 (48.37)	2,558 (49.74)		
45-54	1,807 (36.42)	1,917 (37.27)		
>=55	553 (11.14)	477 (9.27)		
Physician's specialty				
Endocrinology	1,365 (27.51)	1,468 (28.54)		
Cardiology	134 (2.70)	162 (3.15)		
Family Medicine	809 (16.30)	809 (15.73)		
General Medicine	1,248 (25.15)	1,173 (22.81)		
Other	1,406 (28.34)	1,531 (29.77)		

NTD: New Taiwan Dollars; DCSI: Diabetes Complications Severity Index

Table 4. Relative hazards of *stroke* in relation to patient's sex, according to diabetes status

Characteristics	No. of people	Person-years followed	Stroke		Adjusted HR(95%CI)[a]	Adjusted HR(95%CI)[b]
			No. of cases	Incidence density, per 1000 person-years (95% CI)		
Non-Diabetes						
Gender						
Male	19569	184086.19	2698	14.66 (14.10-15.21)	1.287 (1.217-1.361)[a]	
Female (Ref.)	20235	195903.96	2722	13.89 (13.37-14.42)	1.000	
Type 2 diabetes						
Gender						
Male	4,962	40,603.19	1,202	29.60(27.93-31.28)	1.248 (1.146-1.360) [b]	1.250 (1.147-1.362) [c]
Female (Ref.)	5,143	43,478.81	1,204	27.69 (26.13-29.26)	1.000	1.000

[a] Based on Cox proportional hazard regression with adjustmest for age, sex, hypertensive, obesity, income categories, urbanization status, household median income, diabetes complications severity index(DCSI)

[b] Based on Cox proportional hazard regression with adjustmest for age, sex, hypertensive, obesity, income categories, urbanization status, household median income, diabetes complications severity index(DCSI), P4P, prevalence or incidence case, continuity of care index(COC), medication possession ratio (MPR),hospital-level, ownership

[c] Based on Cox proportional hazard regression with adjustmest for age, sex, prevalence or incidence case, continuity of care index(COC), medication possession ratio (MPR), hypertensive, obesity, P4P, income categories, urbanization status, household median income, diabetes complications severity index(DCSI), hospital-level, ownership, physician gender, physician age, division

附件五

國科會補助專題研究計畫出席國際學術會議心得報告

日期：107 年 8 月 15 日

計畫編號	MOST 106-2629-B-006-002		
計畫名稱	建立糖尿病性別差異性健康照護決策支援系統		
出國人員姓名	李中一	服務機構及職稱	成功大學醫學系公共衛生學科暨研究所 / 教授
會議時間	2018 年 3 月 7 日至 2018 年 3 月 10 日	會議地點	義大利、弗羅倫斯
會議名稱	(中文) 第 18 屆婦科內分泌學會國際會議 (英文) The International Society for Gynecological Endocrinology (ISGE), The 18th World Congress,		
發表題目	(中文) 台灣空氣污染與妊娠糖尿病發生之病例對照研究 (英文) A nationwide case-control study of gestational diabetes mellitus in association with air pollution in Taiwan		

一、參加會議經過

第第 18 屆婦科內分泌學會國際會議於 2018 年 3 月 7-10 日於義大利弗羅倫斯舉行，本屆會議的主題是「*Intracrinology: the open door to the future*」，強調女性荷爾蒙研究的未來與創新，在開幕演講中，受邀講員分別從停經後婦女賀爾蒙與健康問題、婦科內分泌醫學的展望、到提升婦女對內分泌與健康的健康識能等面向，討論婦科內分泌的議題。這其中，除了醫學技術的討論外，更是強調醫學教育，及一般教育對於提升婦女健康的重要性。面對婦科內分泌醫學與婦女健康所面臨的健康挑戰，許多本次會議的研究報告，其議題均期望能夠提出創新的解決方案，期望對於全球婦科內分泌相關疾病之預防策略與醫療保健提供重要的建言。此次會議同時也提供全球網路化中健康產業意見領袖以及健康照護提供者及豐富的科學研究數據。 除此之外，許多製藥和生物科技行業，醫療科技及醫療器械公司、諮詢公司、臨床研究組織和資料管理公司也展示了他們有關婦科內分泌學的產品以及服務。

二、與會心得

本次會議總共有 731 篇論文透過口頭或海報的方式進行成果發表。本次會議的議題相當多元，從賀爾蒙與避孕議題、卵巢腫瘤的發生與治療、多囊性卵巢症候群婦女從受孕到生產的健康照護議題、早產與流產預防、產科與內分泌科整合性照護實務與展望、人工生殖、壓力與婦女下視丘病變議題、賀爾蒙與乳癌、以及婦科內分泌疾病之另類醫療都包括在各個場次的演講主題中。

本次會議所討論的議題當中，許多研究都聚焦卵巢功能不全(Premature Ovarian Insufficiency, POI)進行討論，POI 的病因有可能為內源性也有可能為外源性，不過，在許多情況下原因都是不明的。本文目的為整合 POI 長期追蹤的結果。研究的發現大致指出，卵巢類固醇合成缺乏會對婦女的健康造成嚴重的影響，短期造成的影響與自發性的停經症狀相似，主要為更年期症候群，長期觀察來看，POI 造成身體各方面的影響，包括它明顯會大大地降低懷孕的機會，雌激素的缺乏也會造成泌尿生殖器官的萎縮。而最常見的泌尿生殖系統症狀包含陰道乾燥、陰道刺激搔癢，而泌尿道生殖器的萎縮與雌激素的缺乏也會對性功能造成影響。此外，POI 患者也會有固密度降低的風險，罹患 POI 的女性同時必須承受心理歷程的困擾，部份研究顯示也會提高神經性退化疾病的風險。總而言之，罹患 POI 的女性主要會因為心血管疾病產生使預期壽命縮短，另一方面，部份研究則是指出這類患者罹患乳腺癌的風險會降低。許多研究都指出，罹患 POI 的女性患者有一些明顯的健康風險，對於每個病患，應該採取個別的治療方法來辨別並降低這些疾病的風險。

另一討論較多的議題則是赫爾蒙替代療法的致癌風險問題。從美國大多數的觀察性研究資料顯示，賀爾蒙替代療法和乳癌的發生風險，在 1995 年之前的研究中，研究族群包含了使用極高劑量的雌激素作為第一線治療的人群，且在少數女性之中添加了黃體激素。整體而言，每年使的相對危險性上升了 0.023 倍，(分別在 5 年或 10 年內治療的 1000 名女性中，有 2-6 位絕對超過風險)。於 2000 年以後更多美國的研究發表，使用較低劑量雌激素的人群，每年僅增加 0.01 倍的風險；進一步的分析與研究，均未發現在體重過重的女性身上有風險增加的情形，可能的原因是因為，體重過重的女性本身已產生大量雌激素刺激自己的乳房。另外一種解釋可能是口服雌激素，透過其肝臟細胞的作用，反轉肥胖一些生物學上的特徵（例如減少性荷爾蒙與球蛋白的鍵結，和增加胰島素生長因子 I 的活性)，這會潛在的增加了乳癌發生的風險，以平衡雌激素的刺激。研究也指出單獨使用雌激素和少部分人使用雌激素加黃體激素，與乳癌發生發險之間並未存在顯著的差異。相對的，瑞典的研究和最近美國的研究表明，與只使用雌激素相比，添加黃體激素的使用可能會有更高的風險。而黃體酮與黃體激素，對乳房組織在生物學上的作用是有爭議的，即使觀察到的風險增加可能部分歸因於某些非黃體酮類的效果(例如:口服雌激素與肝臟細胞的拮抗）以及（在美國的研究中)，黃體酮類引起的危害作用的影響還沒有被排除。然而，理論上是存在著可能性的，即低劑量的口服雌激素加上黃體激素，僅提供類黃體酮的效果，這顯示了與乳癌發生風險增加的相關性是有限制的。

由於許多因素都會影響婦女內分泌相關的疾病發生風險，會議期間，個人也與義大利、德國、美國研究人員交換糖尿病對於停經後婦女內分泌疾病負擔衝擊的研究心得交換意見。個人於會議中發表「台灣空氣污染與妊娠糖尿病發生之病例對照研究」的學術論文，本論文是本次會議中少數討論環境議題對婦女內分泌疾病影響的研究，因此也吸引到不少會議參與者的興趣，而此論文為利用我國全國性健康資料所進行的研究，多位會議參與者對於我國全民健保資料作為臨床與流行病學研究材料的潛力也深感興趣。

三、發表論文摘要

Title: A nationwide case-control study of gestational diabetes mellitus in association with air pollution in Taiwan

Objective – Mounting evidence has shown an increased risk of gestational diabetes mellitus (GDM) in association with elevated exposure to air pollution. However, limited evidence is available concerning the effect of specific air pollutant(s) on GDM incidence. This study aimed to investigate the respective effect of exposure to individual air pollutant at pre- and post-conception periods on GDM incidence.

Methods – A case-control study design was used in which both cases and controls were selected from a cohort of one million people randomly selected from all beneficiaries registered with Taiwan's National Health Insurance program in 2005.

Participants – Totally 6,717 mothers with GDM diagnosed in 2006-2013 and 6,717 control mothers free from GDM were selected by matching on age and year of delivery.

Intervention – N.A.

Main Outcome – GDM

Measures – Maternal exposures to mean daily air pollutant concentration, derived from 76 fixed air quality monitoring stations, within the 12-week period prior to pregnancy, as well as during the 1st and 2nd trimesters, respectively were assessed by the spatial analyst method (i.e., ordinary kriging) with the ArcGIS. Information on GDM diagnosis was derived from medical claims with ICD-9-CM code: 648.0 or 648.8.

Results – After controlling for potential confounders and other air pollutants, an increase in pre-pregnancy exposure of 1 inter-quartile range (IQR) for $PM_{2.5}$ and SO_2 was found to associate with a significantly elevated odds ratio (OR) of GDM at 1.10 (95% confidence interval (CI) 1.03-1.18 and 1.37 (95% CI 1.30-1.45), respectively. Exposures to $PM_{2.5}$ and SO_2 during the 1st and 2nd trimesters were also associated with significantly increased ORs, which were 1.09 (95% CI 1.02-1.17) and 1.07 (95% CI 1.01-1.14) for PM2.5, and 1.37 (95% CI 1.30-1.45) and 1.38 (95% CI 1.31-1.46) for SO_2. No significant associations of GDM with O_3 or NO_2 were observed

Conclusions – It was concluded that higher pre- and post-pregnancy exposures to $PM_{2.5}$ and SO_2 for mothers were associated with a significantly, but modestly elevated risk of GDM.

keywords: air pollution; gestational diabetes mellitus; nested case-control study; dose-response relationship

四、建議

許多婦女的疾病都與賀爾蒙問題息息相關，特別是停經前後內分泌系統的功能改變，使得停經後婦女健康議題受到研究上許多的重視。本次會議討論議題頗多，而因為許多好發於婦女族群的癌症，發生年齡均有逐年下降的現象，使得育齡期婦女罹患這癌症的議題也逐漸受到重視，因為這不單是婦女健康的議題，也牽涉到子代健康以及是治療取捨，及是否終止妊娠等倫理問題。罹患癌症婦女的當時與後續生育問題牽涉層面廣泛，通常需要許多專業提供協助，包括家庭醫師，腫瘤科醫師，產科醫師，放射線科醫師等專業，而這些多科團隊治療的目的就是要提共這些罹癌婦女的生育能夠獲得最為妥善的照顧與懷孕結果。部分會議論文的內容顯示，這個議題在歐美國家已有許多討論，反觀台灣，從文獻搜尋中這個議題比較少有研究者進行討論。

我國全民健保資料在過去數年期間作為研究素材有很好的論文發表成績，衛福部統計處近年也都陸續規劃加強這些行政資料的加值應用，包括結合健保與臨床、疫苗、癌登、死因等資料庫，以及國內以族群為基礎之全國性調查研究資料（如，國民健康調查、物質使用調查等）；善加利用這些資料，相信可以在婦女內分泌健康相關議題上產生更好的科學知識，做為公共衛生政策或轉譯醫學之重要參考依據，期能更進一步增進民眾的健康，在這方面，北歐國家的經驗值得我們借鏡。

五、攜回資料名稱及內容

「第 18 屆婦科內分泌學會國際會議」論文集。

六、其他

會議參與證明、論文海報發表之相片。

The following abstract has been presented at "Gynecological Endocrinology the 18th World Congress" held in Florence, Italy from 7 to 10 March 2018

Presenter: Chung-Yi Li

P194. A nationwide case-control study of gestational diabetes mellitus in association with air pollution in Taiwan

Objective ? Mounting evidence has shown an increased risk of gestational diabetes mellitus (GDM) in association with elevated exposure to air pollution. However, limited evidence is available concerning the effect of specific air pollutant(s) on GDM incidence. This study aimed to investigate the respective effect of exposure to individual air pollutant at pre- and post-conception periods on GDM incidence. Methods – A case-control study design was used in which both cases and controls were selected from a cohort of one million people randomly selected from all beneficiaries registered with Taiwan's National Health Insurance program in 2005. Participants – Totally 6,717 mothers with GDM diagnosed in 2006-2013 and 6,717 control mothers free from GDM were selected by matching on age and year of delivery. Intervention – N.A. Main Outcome – GDM Measures – Maternal exposures to mean daily air pollutant concentration, derived from 76 fixed air quality monitoring stations, within the 12-week period prior to pregnancy, as well as during the 1st and 2nd trimesters, respectively were assessed by the spatial analyst method (i.e., ordinary kriging) with the ArcGIS. Information on GDM diagnosis was derived from medical claims with ICD-9-CM code: 648.0 or 648.8. Results – After controlling for potential confounders and other air pollutants, an increase in pre-pregnancy exposure of 1 inter-quartile range (IQR) for PM2.5 and SO2 was found to associate with a significantly elevated odds ratio (OR) of GDM at 1.10 (95% confidence interval (CI) 1.03-1.18 and 1.37 (95% CI 1.30-1.45), respectively. Exposures to PM2.5 and SO2 during the 1st and 2nd trimesters were also associated with significantly increased ORs, which were 1.09 (95% CI 1.02-1.17) and 1.07 (95% CI 1.01-1.14) for PM2.5, and 1.37 (95% CI 1.30-1.45) and 1.38 (95% CI 1.31-1.46) for SO2. No significant associations of GDM with O3 or NO2 were observed Conclusions – It was concluded that higher pre- and post-pregnancy exposures to PM2.5 and SO2 for mothers were associated with a significantly, but modestly elevated risk of GDM.

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GYNECOLOGICAL ENDOCRINOLOGY
THE 18TH WORLD CONGRESS
7-10 MARCH 2018 FLORENCE, ITALY

Certificate of Attendance

Chung-Yi Li

attended "Gynecological Endocrinology the 18th World Congress"

held in Florence, Italy from 7 to 10 March 2018

Chung-Yi Li presented the following abstracts:

P194. A nationwide case-control study of gestational diabetes mellitus in association with air pollution in Taiwan

by C. Li

during the Poster Session

ISGE GYNECOLOGICAL ENDOCRINOLOGY THE 18th WORLD CONGRESS 7-10 MARCH 2018 FLORENCE, ITALY Chung-Yi Li (Taiwan) Visit www.womenshealthedu.com to get access to the latest data and join the conversation.	ISGE GYNECOLOGICAL ENDOCRINOLOGY THE 18th WORLD CONGRESS 7-10 MARCH 2018 FLORENCE, ITALY OFFICIAL HASHTAG #ISGE2018
Maternal Exposure to Air Pollutants and Risk of Gestational Diabetes Mellitus in Taiwan	

106年度專題研究計畫成果彙整表

計畫主持人：李中一	計畫編號：106-2629-B-006-002-
計畫名稱：建立糖尿病性別差異性健康照護決策支援系統	

成果項目					量化	單位	質化（說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			0	篇	
國內	學術性論文	研討會論文			0	篇	
國內	學術性論文	專書			0	本	
國內	學術性論文	專書論文			0	章	
國內	學術性論文	技術報告			0	篇	
國內	學術性論文	其他			0	篇	
國內	智慧財產權及成果	專利權	發明專利	申請中	0	件	
國內	智慧財產權及成果	專利權	發明專利	已獲得	0	件	
國內	智慧財產權及成果	專利權	新型/設計專利		0	件	
國內	智慧財產權及成果	商標權			0	件	
國內	智慧財產權及成果	營業秘密			0	件	
國內	智慧財產權及成果	積體電路電路布局權			0	件	
國內	智慧財產權及成果	著作權			0	件	
國內	智慧財產權及成果	品種權			0	件	
國內	智慧財產權及成果	其他			0	件	
國內	技術移轉	件數			0	件	
國內	技術移轉	收入			0	千元	
國外	學術性論文	期刊論文			0	篇	
國外	學術性論文	研討會論文			1	篇	Li CY. A nationwide case-control study of gestational diabetes mellitus in association with air pollution in Taiwan. The 18th World Congress of Gynecological Endocrinology, Florence, Italy, March 07-10, 2018.
國外	學術性論文	專書			0	本	
國外	學術性論文	專書論文			0	章	
國外	學術性論文	技術報告			0	篇	
國外	學術性論文	其他			0	篇	
國外	智慧財產權及成果	專利權	發明專利	申請中	0	件	
國外	智慧財產權及成果	專利權	發明專利	已獲得	0	件	
國外	智慧財產權及成果	專利權	新型/設計專利		0	件	
國外	智慧財產權及成果	商標權			0	件	
國外	智慧財產權及成果					件	

		營業秘密	0		
		積體電路電路布局權	0		
		著作權	0		
		品種權	0		
		其他	0		
	技術移轉	件數	0	件	
		收入	0	千元	
參與計畫人力	本國籍	大專生	0	人次	
		碩士生	1		本計畫部分內容為成功大學醫學案公共衛生研究所碩士班李詠心目前正在進行中之碩士論文一部分。李詠馨預計於107學年度第1學期完成學位考試。
		博士生	0		
		博士後研究員	0		
		專任助理	0		
	非本國籍	大專生	0		
		碩士生	1		1位碩士級兼任助理
		博士生	1		1位博士級兼任助理
		博士後研究員	0		
		專任助理	1		1位碩士級專任助理
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）					

科技部補助專題研究計畫成果自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估 ■達成目標 □未達成目標（請說明，以100字為限） 　　□實驗失敗 　　□因故實驗中斷 　　□其他原因 說明：
2. 研究成果在學術期刊發表或申請專利等情形（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊） 論文：□已發表　□未發表之文稿　■撰寫中　□無 專利：□已獲得　□申請中　■無 技轉：□已技轉　□洽談中　■無 其他：（以200字為限）
3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性，以500字為限） 婦女本來有比較低的血管疾病發生率，不過婦女一旦罹患糖尿病後，其所增加的心血管疾病風險則是明顯高於同樣是糖尿病患的男性。此現象除了被歸因於生物學因素外，因為結構性因素輕忽婦女新血管疾病風險，以及婦女本身的行為因素最近也常被討論是造成式性別差異縮小的原因之一。台灣糖尿病盛行率高，衍生醫療資源與疾病負擔亦大，本研究利用本土資料分析、探討影響男女性糖尿病人發生冠狀動脈疾病與中風的結構性與行為因素，研究所的訊息對於預防不同性別糖尿病人心血管疾病發生具有實質的助益。
4. 主要發現 本研究具有政策應用參考價值：■否　□是，建議提供機關 （勾選「是」者，請列舉建議可提供施政參考之業務主管機關） 本研究具影響公共利益之重大發現：□否　□是 說明：（以150字為限）