Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly affects joints with synovium. It predisposes patients to insulin resistance and may place patients at a higher risk for diabetes mellitus (DM). Because DM is a major risk factor for cardiovascular disease (CVD), which is the leading cause of mortality in RA, a better assessment of DM risk in patients with RA may lead to earlier and aggressive intervention to prevent its occurrence, subsequently decreasing mortality for patients with RA.

Inflammation in RA is characterized by increased levels of mediators and cytokines, e.g., tumor necrosis factor-α and interleukin 6 (IL-6), which cause dyslipidemia and accelerate atherosclerosis, resulting in hypertension (HTN). In addition, these cytokines appear to block the function of insulin at the receptor level, which may induce insulin resistance. Mortality from CVD in patients with RA may result from insulin resistance, DM, dyslipidemia, atherosclerosis, or HTN.

Several studies have focused on the risk of DM in RA. Using health insurance data, one study calculated a 1.4 prevalence ratio for diabetes in an RA cohort composed of 28,208 patients compared with the non-RA cohort. In another study, a calculated HR of 1.5 was obtained using linked healthcare use data. However, other studies showed no significant association between RA and T2D.

Taiwan started its compulsory National Health Insurance (NHI) system in 1995. More than 95% of the hospitals and clinics in Taiwan implement the NHI, and more than 98% of the people are covered by this system. The NHI databank is considered reliable.

We used this databank to examine the risk of T2D for patients with RA in Taiwan. In addition, we studied the effects of age, sex, use of glucocorticoids (GC), HTN, disorders of lipid metabolism (DLM), and RA on T2D risk.
MATERIALS AND METHODS
The databank we used contains medical information from 1 million residents in Taiwan, randomly selected by the National Health Research Institute. We removed those who were younger than age 20 years or who had a diagnosis of either T2D or RA by 1998. RA was ascertained by International Classification of Diseases, 9th edition, code 714.0 in at least 3 visits plus at least 2 visits with prescription of antirheumatic drugs in any 12-month period. Medication period must last more than 6 months. This diagnosis plus medication criterion was adopted from a previous report. T2D was ascertained by admission with a T2D code or at least 3 visits with T2D code within 1 year. The criteria were suggested by Lin, et al.

HTN and DLM were identified by admission with HTN and DLM codes (4010, 4011, 4019 for HTN and 2720–2729 for DLM) or at least 3 visits with these codes during the study period. We excluded those who had the diagnosis of T2D prior to the diagnosis of RA.

We then assembled 600,336 subjects (300,135 men and 300,201 women) from the databank. Among them, 3839 had RA (1130 men and 2709 women), and the rest were defined as non-RA. We calculated the age-standardized and age-specific incidence of T2D in RA and non-RA cohorts. Patients with RA were followed up from the diagnosis, and the non-RA from January 1, 1998, until the diagnosis of T2D or the censor events (i.e., dropout from the NHI or the end of 2009).

We defined age as the age in 1998, and a GC user as a person who had at least 3 visits with prescription of GC within 12 months. For the RA cohort, we used the Kaplan-Meier method to estimate the event-free probability of T2D after an RA diagnosis. The log-rank test was used to compare among groups of different ages or sexes. Cox regression was applied to study the effects of RA, HTN, and DLM on T2D risk. The HR for T2D were obtained with the Cox model.

RESULTS
Patients with RA had a higher risk for T2D. Figure 1 and Table 1 show the incidence of T2D in the RA and non-RA
cohorts. Overall, the incidence of T2D increased with age. One exception is that middle-aged men with RA had a higher incidence of T2D than older men with RA. The relative risk of T2D was 1.68 for men with RA and 1.46 for women with RA. The relative risk was higher in the young and middle-aged groups. For older men or women with RA, the effect of RA on the risk for T2D was minimal.

Disease duration and age on the risk of developing T2D. Figure 2A shows the effects of disease duration and age on the risk of developing T2D. As expected, aged people with RA were more likely to develop T2D than younger people with RA. The relative risk was higher in the young and middle-aged groups. For older men or women with RA, the effect of RA on the risk for T2D was minimal.

Sex and the risk of developing T2D. We did not find a significant difference between men and women in the risk of developing T2D for the young adults and older adults. However, there was a significant difference between middle-aged men and women with RA. As shown in Figure 1, middle-aged men with RA were more likely to develop T2D than middle-aged women with RA. Figure 2B shows that for patients with RA, men had a higher T2D hazard than women.

HTN and DLM significantly increase T2D risk. We used Cox regression to study the effects of age, sex, RA, HTN, DLM, and GC use on T2D risk. Table 2 lists the HR obtained from the univariate model and multivariate model with interactions. HTN and DLM are both significantly associated with a higher T2D risk, with HR 2.42 and 4.21, respectively. Comorbidities of both HTN and DLM increased the HR in patients with RA to 22 (95% CI 20–26). The role of GC use. GC use is a strong risk factor for T2D in patients with RA, based on results from both univariate and multivariate models (Table 2). The multivariate model revealed that GC use has significant interactions with HTN and age. HTN without GC use had a higher HR for T2D than HTN with GC use (HR 2.51 vs 2.03). Nevertheless, HTN, DLM, RA, and GC use are all risk factors for T2D.

We used the Wald chi-square test to verify the proportional hazard assumption for the multivariate Cox model. Because of the large difference in sample sizes between the 2 cohorts, the normal procedure for the Wald test could not apply. To overcome the problem, we used a smaller sample, containing 5000 subjects from the non-RA cohort, to meet the proportional hazard assumption with p value 0.223.

DISCUSSION
Patients with RA are reported to carry a higher cardiovascular risk, and there is a gap in our understanding of why such a higher risk exists. In addition, RA patients with DM were less likely to be tested for glycosylated hemoglobin, indicating that rheumatologists need a higher level of awareness of DM and more aggressive intervention. To raise awareness, information is needed on the DM risk for patients with RA and how other clinical factors may modify the risk.

The results of our study, based on a comprehensive national databank, confirm an elevated risk for T2D among patients with RA. T2D incidence increased with age for both men and women. The incidence rate for T2D was higher in men than in women. In both genders, the incidence rate of T2D was higher in the older age groups than in the younger age groups. The incidence of T2D was higher in men with RA than in women with RA.

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For women with RA, there was an increased risk for T2D and decreased relative risk for T2D with age. But for men with RA, the highest risk for T2D and highest relative risk occurred in middle age (40–60 years). The estimated HR of RA to non-RA in the oldest male group was 1.11; however, this was not statistically significant. Older populations are more likely to have multiple diseases, e.g., coronary heart disease or HTN, and to take multiple medicines, e.g., thiazide or β-blockers, thus diluting the risk of RA for T2D in these populations.
Certainly promote early and active intervention from doctors and patients, thus lowering the risk for DM and CVD. The change one’s long-accustomed lifestyle, so patients need a strong motivation. An accurate assessment of the risk can help physicians assess the DM risk for their patients with RA and alert those with a higher risk to lead a healthy lifestyle, thus taking aggressive preventive measures. At the same time, physicians are also urged to take measures, e.g., to test glycosylated hemoglobin.

**ACKNOWLEDGMENT**

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### REFERENCES

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### Table 2. Hazard ratios (HR) for type 2 diabetes from Cox regression, for effects of RA, hypertension (HTN), disorder of lipid metabolism (DLM), and GC usage.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate HR (95% CI)</th>
<th>p</th>
<th>Risk Factor</th>
<th>Multivariate HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (male = 1 vs female = 0)</td>
<td>1.046 (1.045–1.046)</td>
<td>&lt; 0.0001</td>
<td>Age (male = 1 vs female = 0)</td>
<td>1.031 (1.031, 1.032)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RA (yes = 1 vs no = 0)</td>
<td>2.37 (2.15–2.60)</td>
<td>&lt; 0.0001</td>
<td>RA (yes = 1 vs no = 0)</td>
<td>2.40 (2.18, 2.63)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HTN (yes = 1 vs no = 0)</td>
<td>6.79 (6.67–6.90)</td>
<td>&lt; 0.0001</td>
<td>HTN (yes = 1 vs no = 0)</td>
<td>2.51 (2.46, 2.56)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DLM (yes = 1 vs no = 0)</td>
<td>8.03 (7.90–8.17)</td>
<td>&lt; 0.0001</td>
<td>DLM (yes = 1 vs no = 0)</td>
<td>4.21 (4.13, 4.28)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>GC (yes = 1 vs no = 0)</td>
<td>1.31 (1.28–1.35)</td>
<td>&lt; 0.0001</td>
<td>GC (yes = 1 vs no = 0)</td>
<td>1.34 (1.22, 1.047)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Non-GC HTN vs non-HTN</td>
<td>2.51 (2.46, 2.56)</td>
<td>&lt; 0.0001</td>
<td>Non-GC HTN vs non-HTN</td>
<td>2.51 (2.46, 2.56)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; HTN: hypertension; GC: glucocorticoids.


