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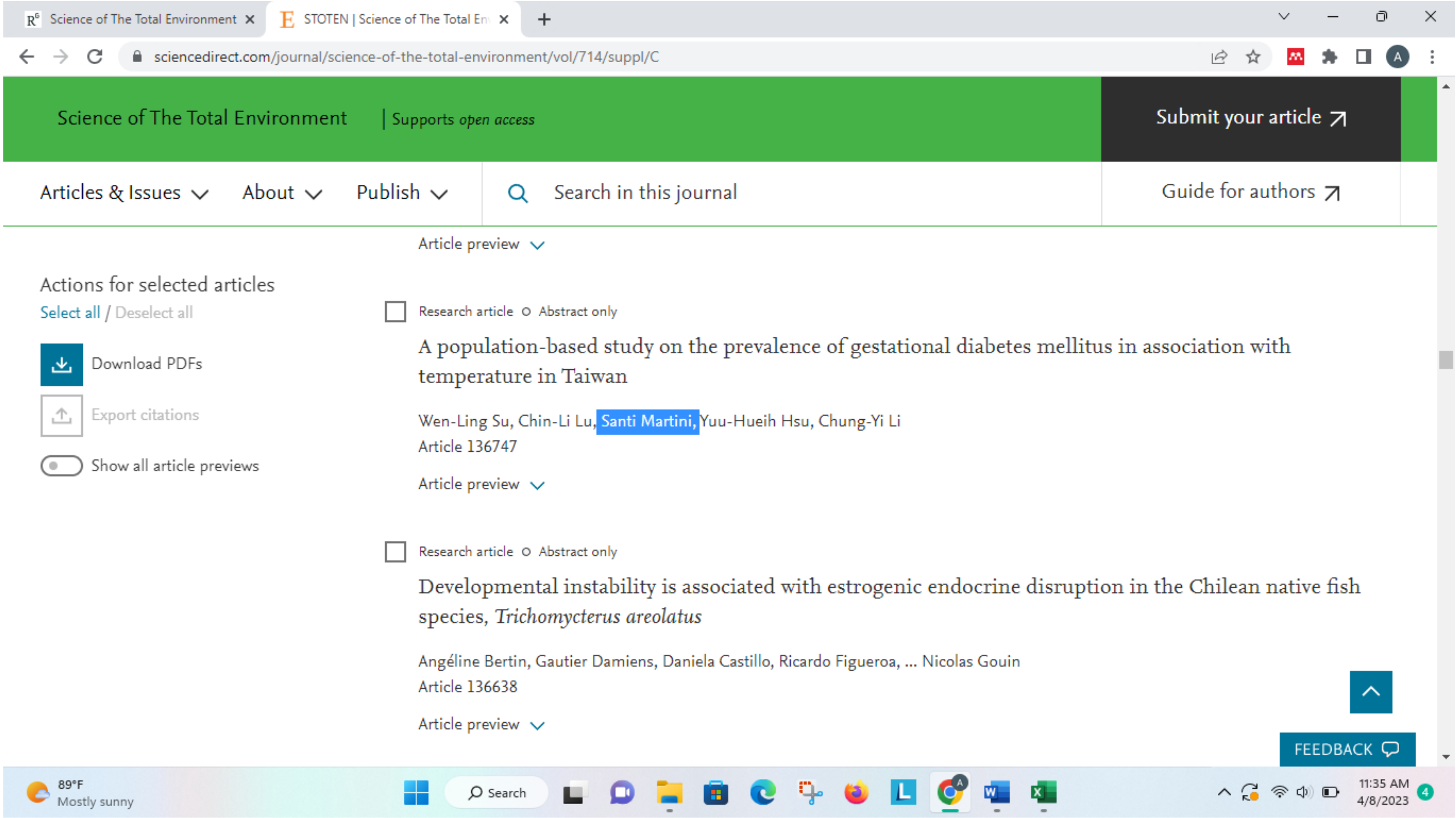

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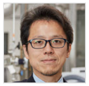

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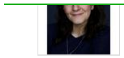

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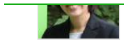

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National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, United States of America

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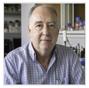

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Institute of Marine Science of Andalucia, Department of Ecology and Coastal Management, Puerto Real, Spain

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Zhengzhou University, Zhengzhou, China

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University of Birmingham, Birmingham, United Kingdom

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Zhen (Jason) He

Washington University in St. Louis, Department of Energy, Environmental and Chemical Engineering, St. Louis, Missouri, United States of America

Water pollution and treatment, Environmental biotechnology, Resource recovery from wastes, Bioelectrochemical systems, Bioenergy, Membrane technology, Bioremediation, Desalination

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Utrecht University, Utrecht, Netherlands

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Duke University, Durham, North Carolina, United States of America

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Barbara Hoffmann

University Hospital Dusseldorf Centre for Health and Society, Dusseldorf, Germany

Research Interests: Air pollution, noise, cardiovascular dieasese, metabolic and neurocognitive impairment

Milena Horvat

Jozef Stefan Institute, Ljubljana, Slovenia

Radionuclides, essential and potentially toxic elements metals, speciation, mercury, environment and health, biogeochemistry, marine environment, metrology contaminated sites, food contaminants, ,

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Institute of Earth Physics of Paris, Paris, France

Guangming Jiang

University of Wollongong, School of Civil, Mining and Environmental Engineering, Wollongong, Australia

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West Virginia University, Morgantown, West Virginia, United States of America

Water quality, Health, Forecasting, Water resources, Remote sensing, Statistical modelling, Climate change, Infectious disease

Kurunthachalam Kannan

New York University, Department of Pediatrics, New York, New York, United States of America

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LaKind Associates LLC, Catonsville, Maryland, United States of America

Biomonitoring, Risk assessment, Exposure to chemicals, Systematic reviews, Data quality

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United States Environmental Protection Agency, Washington, District of Columbia, United States of America

Developmental toxicology, birth defects research, developmental origins of health and diseases

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Robert Letcher

Environment and Climate Change Canada, Gatineau, Quebec, Canada

Analytical chemistry and method development, and environmental and forensic chemistry of established ("legacy") and emerging organic contaminants in wildlife and fish Bioaccumulation, fate and trophodynamics of established and emerging contaminants and metabolites in wildlife (e.g., top predators), food webs, and aquatic ecosystems (e.g., Arctic and Great Lakes). Mechanistic and

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Fudan University, Shanghai, China

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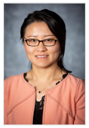

Jing Li

South China Agricultural University, Guangzhou, China

Emerging contaminants and degradation, Environmental chemistry, Ecotoxicology, Human biomonitoring and health outcomes

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Jinhua Li

Jilin University, Changchun, China

Water Disinfection byproducts, Analytical and Environmental Toxicology, Public health, Water and food safety, Emerging contaminants

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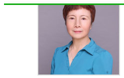

Lena Q. Ma

Zhejiang University College of Environmental and Resource Sciences, Hangzhou, China

Biogeochemistry of trace metals, Phytoremediation and hyperaccumulation, Bioavailability and bioaccessibility, Human health and food safety, Plant metal uptake, Rhizosphere chemistry, Root exudates, Microbial transformation of metals, Metal transports in plants, Metal detoxification in plants and microbes

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Nancy Bixian Mai

Institute of Geochemistry Chinese Academy of Sciences, Guiyang, China

Persistent organic pollutants (POPs); Bioaccumulation; atmosphere; Sediment; Environmental fate and transfer; Exposure and risk assessment

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Konstantinos C. Makris

Cyprus University of Technology Cyprus International Institute for Environmental and Public Health, Lemesos, Cyprus

Human exposome, environmental health, non-pharmacological trials, metabolomics

New South Wales, Department of Planning and Environment, Sydney, Australia

Urban air quality; Human and environmental exposures; Green spaces and their health impacts

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Lidia Mínguez-Alarcón

Harvard Medical School, Boston, Massachusetts, United States of America

Endocrine disrupting chemicals, Chemical mixtures, Diet-chemical interactions, Reproductive epidemiology, Human infertility, Cardiovascular Disease

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University of Georgia, Athens, Georgia, United States of America

David Oliver

University of Stirling, Stirling, United Kingdom

Diffuse microbial pollution from agriculture; modelling & decision support in environmental systems; fate & transfer of human pathogens; recreational water quality

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Biotransformation; Bioremediation; Bioenergy and biofuels; Bioelectrochemical systems; Kinetics and modeling

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Hui Peng

University of Toronto, Toronto, Ontario, Canada

Analytical environmental chemistry, Toxicology, Nontargeted analysis, Proteomics, Chemical pollutants

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Nuno Ratola

University of Porto, Porto, Portugal

Environmental presence and behaviour of legacy and emerging organic contaminants; Biomonitoring and chemical transport of chemicals; Advanced analytical techniques of extraction and quantification; Field sampling campaigns and sample handling protocols; Exposure assessment and prioritisation of relevant compounds; Climate change scenarios

Benoit Roig

University of Nîmes, Nimes, France

New approach methods (NAMs), Tissue chip, In vitro toxicology models, Regulatory science

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Matthew Scotch

Arizona State University Biodesign Center for Environmental Health Engineering, Tempe, Arizona, United States of America

Molecular epidemiology, Genomic epidemiology, RNA viruses, bioinformatics, public health surveillance, influenza

Heqing Shen

Institute of Urban Environment Chinese Academy of Sciences, Xiamen, China

Biological monitoring (Bio-monitoring); Endocrine disrupting chemicals; Human microbiome; Birth cohort; Male fertility; Biomarkers; Epigenetics; OMICS with emphasis toxicometabolomics

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Luis Felipe Silva Oliveira

University Corporation of the Coast, Department of Civil and Environmental Engineering, Barranquilla, Colombia

Christian Sonne

Aarhus University, Department of Environmental Science, Roskilde, Denmark

Biological effects, environmental chemicals, infectious diseases, climate change, veterinary science, wildlife medicine, predatory mammals, raptorial birds, sea birds, fish, internal organs, reproductive organs, histopathology, morphology, skeletal system, bone density, immune system, endocrinology, PBPK modelling, blood biochemistry, implantation of PTT satellite transmitters, immobilization.

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Massimo Stafoggia

Local Health Authority Rome 1, Department of Epidemiology, Roma, Italy

Exposure assessment; statistical methods; air pollution; epidemiology; study design

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Heather Stapleton

Duke University, Durham, North Carolina, United States of America

Environmental Chemistry, Human Exposure, Children's Environmental Health, Metabolism and Biotransformation, Halogenated Persistent Pollutants, Endocrine Disruptors, Flame Retardant Use & Exposure, In Vitro Assays for Thyroid Disruption.

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VU Amsterdam, Amsterdam, Netherlands

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Nanjing University of Science and Technology, Nanjing, China

Analytical Chemistry, Ecotoxicology, Molecular Toxicology, Environmental Monitoring, Risk Assessment, Human studies, Organic Contaminates, Flame Retardants, Urinary Biomarkers, Metabolites, Gas Chromatography-Mass Spectrometry (GC-MS), Lipid Chromatography-Mass Spectrometry (LC-MS)

Shengzhi Sun

Boston University School of Public Health, Boston, Massachusetts, United States of America

Environmental Health, Environmental Epidemiology, Air Pollution, Climate Change, Climate Hazards, Risk Assessment, prenatal epidemiology

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National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China

Environmental epidemiology, climate change, planetary health, sustainable development, quantitative risk assessment, spatiotemporal modelling

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University of Cadiz, Cadiz, Spain

Mar Viana

Institute of Environmental Assessment and Water Research, Barcelona, Spain

Indoor and outdoor air pollution, air quality, impacts on health, burden of disease, incidental and engineered nanoparticles, ultrafine particles, personal exposure, workplace exposure, industrial workplaces, mitigation strategies, environmental policy, source apportionment, sensor technologies

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Tongji University, Shanghai, China

Modelling &, decision support in environmental systems, Urban and regional water quality, Water pollution control of river system, Urban sewage system planning, Aquatic Ecosystem management

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The University of Texas Health Science Center at Houston, Department of Epidemiology Human Genetics and Environmental Sciences, Houston, Texas, United States of America

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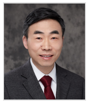

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Tsinghua University School of Architecture, Beijing, China

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A population-based study on the prevalence of gestational diabetes mellitus in association with temperature in Taiwan

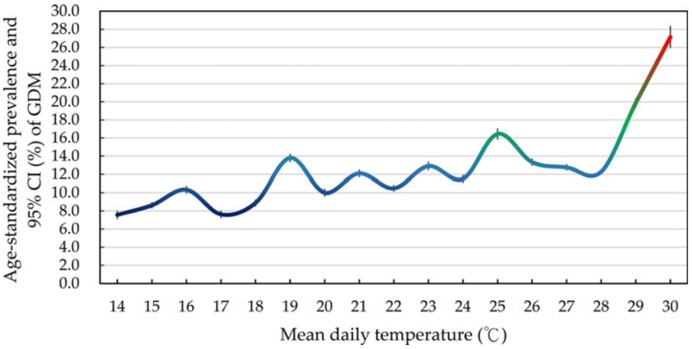
Wen-Ling Su [a,1], Chin-Li Lu [b,1], Santi Martini [c], Yuu-Hueih Hsu [a], Chung-Yi Li [a,c,d,e,*]

[a] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Graduate Institute of Food Safety, College of Agriculture and Natural Resources, National Chung Hsing University, Taichung, Taiwan*
[c] *Department of Epidemiology, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia*
[d] *Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan*
[e] *Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan*

HIGHLIGHTS

- Little is known about the link of specific temperature with GDM, especially in sub-tropical areas.
- This cohort study used a national birth notification and monitoring temperature data.
- Both atmosphere (temperature) and biosphere (GDM) parameters are involved.
- GDM increased with increasing mean daily temperature, especially at >28 °C.
- Prevalence of GDM declined with increasing within-day difference in temperature.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Previous studies showing seasonal clustering of gestational diabetes mellitus (GDM) were conducted in the temperate or frigid zones and mostly included pregnant Caucasian women. This study aims to investigate the association of ambient temperature with prevalence of GDM in Taiwan, a sub-tropic country.
Methods: This population-based cohort study comprised women ($n = 371{,}131$) who gave births between 2013 and 2014; of which, 43,538 (11.7%) were diagnosed with GDM. The mean daily temperature and difference in temperature within a day was calculated over a 35-day period prior to GDM diagnosis or the first day of the 27th gestational week (for non-GDM subjects). Multiple logistic regression models with generalized estimation equation were performed to estimate the adjusted odds ratio (aOR) and 95% confidence interval (CI) of GDM in association with temperature.
Results: After controlling for potential confounders, summer and fall were associated with higher risk of GDM diagnosis, with aOR [95% CI] of 1.05 [1.04–1.07] and 1.04 [1.02–1.06] in reference to winter. Additionally, an increase of 1 °C from 14 °C to 27 °C was associated with an aOR of 1.03 [1.02–1.03]. The aOR greatly increased to 1.54 [1.48–1.60]

Abbreviations: aOR, adjusted odds ratio; APC, annual percentage change; CCI, Charlson's comorbidity Index; CI, confidence interval; GDM, gestational diabetes mellitus; NHI, National Health Insurance; NHIA, National Health Insurance Administration; PCOS, polycystic ovary syndrome; SES, socio-economic status..

[*] Corresponding author at: Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, #1, University Rd., Tainan 701, Taiwan.
E-mail address: cyli99@mail.ncku.edu.tw (C.-Y. Li).

[1] Wen-Ling Su and Chin-Li Lu contribute equally to this article.

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after 28 °C. An increase of 1 °C difference within a day was associated with a reduced aOR at 0.90 [0.87–0.92].
Conclusion: A higher prevalence of GDM was associated with a higher daily temperature, but with a smaller difference in temperature within a day.

1. Introduction

The potential seasonality of gestational diabetes mellitus (GDM) was previously studied in Southern Australia (Moses and Griffiths, 1995) and the UK (Janghorbani et al., 2006). Both studies found the higher prevalence of GDM in summer and in certain months with high temperatures; however, the tendency of seasonality observed did not reach statistical significance. Several recent studies found seasonal clustering of GDM with a higher prevalence in summer (Chiefari et al., 2017; Katsarou et al., 2016; Moses et al., 2016; Vasileiou et al., 2018). Rather than investigating the concurrent relationship between season and GDM, the study by Verburg et al. (2016) examined the incidence of GDM in relation to the season of the estimated date of conception (eDoC); the results demonstrated the presence of a peak incidence among pregnancies with eDoC in winter. Apart from the examination of seasonality pattern, Booth et al. (2017) explored the prevalence of GDM in relation to specific temperature and found that each 10 °C increase in mean 30-day temperature prior screening was associated with a 1.06 (95% CI 1.04–1.07) times higher odds of GDM. In a later report, Vasileiou et al. (2018) found that at temperatures above 25 °C, the average glucose 60-min and 120-min levels increased; and the relative risk for abnormal glucose values at 60 min, when the environmental temperature increased over 25 °C, increased at 2.2 (95% CI 1.5–3.3).

All these studies were conducted in the temperate or frigid zones (Australia, Greece, Italy, Sweden, and UK) and mostly included pregnant Caucasian women. For example, the minimum and maximum temperatures examined in the Canadian study by Booth et al. (2017) were ≤ −10 °C and ≥ 24 °C, respectively. Although the Greek study by Vasileiou et al. (2018) was conducted at higher temperatures, it included only 768 women, and only 193 (25.1%) were screened for GDM at temperature ≥ 30 °C. Despite the difficulty in making comparison due to dissimilarity in diagnostic criteria, data showed obvious global variation in GDM prevalence; that is, regions near the equator, such as Middle East and North Africa, South East Asia, and Western Pacific, showed higher prevalence (Zhu and Zhang, 2016). Generalizability of the currently available findings to other regions may not be so straightforward. Thus, we conducted this population-based study that included all pregnant women in Taiwan, a sub-tropic country, in 2013 and 2014 to further assess the prevalence of GDM in association with season and temperature.

2. Materials and methods

The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (No. B-ER-107-014).

2.1. Data source

We used health data from two national datasets supervised by the Health and Welfare Data Science Center, Ministry of Health and Welfare, including Birth Notifications (2013–2014), and medical claims of the National Health Insurance (NHI) program (2013–2014). The Birth Notifications provided information on demographic characteristics and place of living at delivery of mothers, as well as birth characteristics such as stillbirth, birthweight, gestational age, congenital abnormalities, and Apgar scores (Chou et al., 2016). Most gynecologists in Taiwan directly calculate the days since the beginning of the last menstrual period to estimate gestational age. The NHI dataset is a medical claim database that covers medical records of nearly all (>99%) Taiwanese residents, and the National Health Insurance Administration performs quarterly expert reviews on a random sample of medical claims to ensure their accuracy (Wen et al., 2018).

2.2. Study design and sample

A cohort of 404,864 deliveries involving 391,992 mothers and 411,736 offspring was identified from the Birth Notifications in 2013 and 2014. We excluded those deliveries with missing mother's ID ($n = 6$), gestational age < 28 or > 42 weeks ($n = 4809$), mothers aged<15 or > 50 years ($n = 82$), or mothers residing on remote islands ($n = 3002$), where no meteorological monitoring stations (MMSs) were available. We did not make further exclusion of potential confounders such as parity, singleton/multiple births, prior history of GDM, and co-morbidity was to preserve as much as information of the entire mother population, which is also essential to the generalizability of study findings.

After linking to NHI medical claims, we further excluded deliveries with mothers whose IDs were not found in the NHI Beneficiary Registry ($n = 7543$) and mothers who had a history of diabetes (ICD-9-CM: 250) in medical claims prior to GDM diagnosis (for GDM mothers) or index date (for non-GDM mothers) ($n = 18,291$). We obtained 371,131 deliveries involving 360,761 mothers and 377,289 offspring (Fig. 1). Among all deliveries, 43,538 were coded with GDM (ICD-9-CM: 648.0 or 648.8). In clinical practice of Taiwan, both Carpenter and Coustan's criteria and the criteria proposed by the International Association of the Diabetes and Pregnancy Study Group were accepted by the NHI program as diagnostic strategies for determining GDM (Wu et al., 2016). The choice is dependent upon the preference of both mothers and obstetricians. The index date was the date of GMD diagnosis for mothers with the disease or the first day of the 27th weeks of gestation (for non-GDM subjects) when the GDM screening was scheduled to perform according to the NHI guideline for non-GDM women (Shen et al., 2017).

2.3. Assessment of ambient temperature

Meteorological data (2012–2014) were provided by the Central Weather Bureau of Taiwan. Taiwan has 21 MMSs, and each of these stations records a variety of meteorological data every hour, including temperature, relative humidity, wind velocity, and precipitation. We categorized all MMSs according to their geographic locations, namely, North ($n = 7$), Central ($n = 4$), South ($n = 4$), and East ($n = 6$).

We calculated two temperature exposure parameters. One parameter was the *daily temperature*, which was averaged from all hourly reading of all MMSs in a specific area. The other parameter was the *within-daily difference in temperature*, estimated from the difference between maximum and minimum temperature in a day. We further calculated both mean daily temperature and mean within-day difference in temperature across different time periods (7, 14, 21, 28, and 35 days) prior to GDM diagnosis and index date. The correlations of mean daily temperature calculated from different time periods are shown in Supplemental Table 1. Considering the correlation coefficients between the 35-day mean daily temperature and mean daily temperature of the other time periods are considered high, we decided to use the 35-day mean daily temperature as the exposure measure in this study to obtain a more stable estimate of temperature exposure. Separate analysis of mean daily temperature and mean within-day difference in

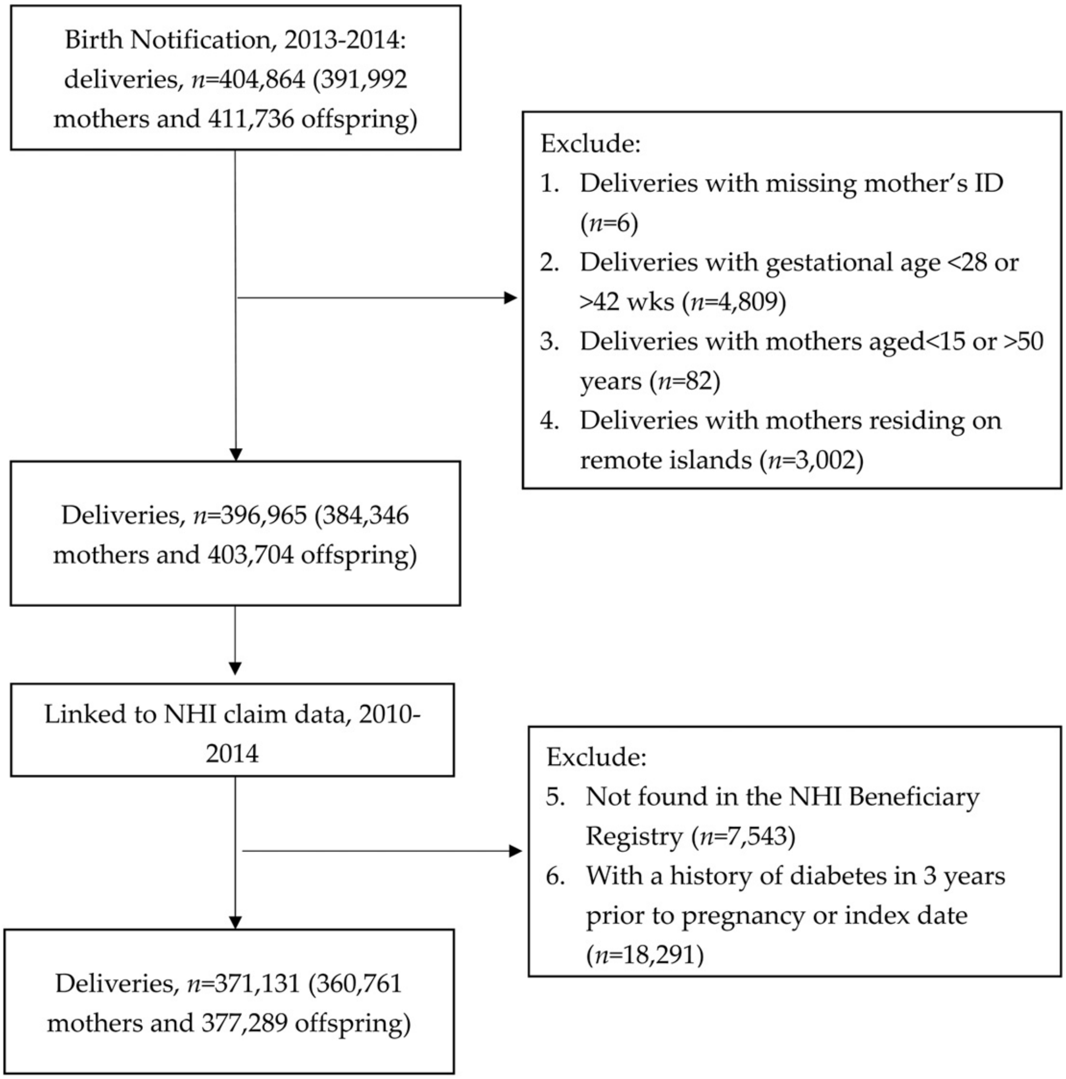


Fig. 1. Flow chart of study sample enrollment. Abbreviations: NHIA, National Health Insurance Administration.

temperature in associated with GDM was due to a low correlation coefficient ($r = 0.12$) between the two parameters estimated for the 35-day period before GDM. In fact, the time trend of mean daily temperature and that of mean within-day difference in temperature calculated from 7, 14, 21, 28, and 35-day period, respectively were very dissimilar (Supplemental Fig. 1). Moreover, unlike the mean daily temperature that is consistently higher in summer season, the mean within-day difference in temperature shows no regular pattern of seasonal variation in Taiwan (Supplemental Fig. 2).

2.4. Covariates

Socio-demographic characteristics of mothers were abstracted, including age, country of birth, parity urbanization level of residence, monthly-income-based insurance premium, and low-income family. Age was determined on the index date. The NHI Beneficiary Registry provides information of low-income family, for which the insurance premium can be waived. We categorized all 316 city districts of a mother's residence into four geographic locations, namely, North, Central, South, and East. The classification scheme used to determine the level of urbanization for each district was proposed by Liu et al. (2006), who classified all districts in Taiwan into clusters according to 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. Although the above-mentioned monthly-income-based insurance premium was considered as person-level socio-economic status (SES) indicator, we used district-specific median household income (National Taxes Statistics, 2014) to indicate neighborhood SES. Personal and neighborhood income levels were determined for the year of delivery.

Apart from socio-demographic variables, we also considered certain co-morbidity presumably associated with risk of GDM, including diagnosed obesity (Buchanan et al., 2012), history of polycystic ovary syndrome (PCOS) (Pan et al., 2015; Yu et al., 2016), and disease burden indicated by Charlson's comorbidity Index (CCI) (Charlson et al., 1987).

2.5. Statistical analysis

We calculated the overall and specific crude prevalence of GDM, which was standardized for age by using the WHO 2000 standard population. The age-standardized prevalence of GDM and its 95% confidence interval (CI) were depicted to examine its variation associated with month, season, and mean daily temperature. We also tested for the significance of linear trends in the crude and age-standardized prevalence of GDM in association with daily temperature by using the jointpoint regression model. The model calculated the annual percentage change (APC) in GDM prevalence per 1 °C increase in the mean daily temperature (Kim et al., 2000). Although the age-standardized prevalence of GDM gradually increased with increasing daily temperature, the jointpoint regression model indicated 1 jointpoint at 28 °C (See Supplemental Fig. 3). The APC lower and higher than 28 °C was estimated at 2.79% and 43.86%, respectively. In this regard, we performed multiple logistic regression model separately for women who received GDM screening on days lower than 28 °C and for those who received GDM screening on days of 28 °C and higher. On the other hand, Supplemental Fig. 4 shows jointpoint regression of the relationship between mean within-day difference in temperature and crude (above) and age-standardize (below) prevalence of GDM; and no inflection was found for the inverse relationship observed.

To account for multiple births by the same mother, the effect of temperature was analyzed using logistic regression model with generalized estimating equations methods, specifying an exchangeable structure of a working correlation matrix, to construct regression models, which was conducted to assess the independent associations of month and season, namely, spring (Mar. – May), summer (Jun. – Aug.), fall (Sep. – Nov.), and winter (Dec. – Feb.) with GDM. Data were analyzed using SAS (version 9.4; SAS Institute, Cary, NC).

3. Results

Table 1 shows the overall and specific prevalence of GDM according to the characteristics of study subjects. Although 11.73% study subjects had GDM diagnosis during pregnancy, an obvious variation in GDM prevalence was seen with respect to certain socio-demographic characteristics. Women with a history of polycystic ovary syndrome and GDM as well as those who had higher CCI score also had elevated GDM prevalence.

The crude prevalence of GDM was higher in fall (12.48%) and summer (11.77%) but lower in winter (11.65%) and spring (10.95%) (Table 1). After standardization for age, similar pattern of seasonal clustering of GDM sustained (Fig. 2(a)). The age-standardized prevalence of GDM in each month also showed variation, with a higher prevalence noted from May to October (See Supplemental Fig. 5). Fig. 2(b) shows an increasing trend in age-standardized GDM prevalence with increasing specific temperature, with a notable inflection in GDM prevalence after 28 °C. With respect to the association of mean daily difference in temperature with GDM prevalence, Fig. 3 shows that age standardized prevalence of GDM gradually decreased as the mean within-day difference in temperature increased.

Table 2 shows the crude and adjusted odds ratio (aOR) of GDM diagnosis in association with season of GDM screening and temperature. Compared with winter, summer (aOR 1.05; 95% CI 1.04–1.07) and fall (aOR 1.04; 95% CI 1.02–1.06) were associated with elevated aOR; however, spring (aOR 0.97; 95% CI 0.95–0.99) showed a lower aOR. In addition, per 1 °C increase in the mean daily temperature was associated with a 3% increase in the odds of GDM (aOR = 1.03; 95% CI 1.02–1.03) for mean daily temperature ranging from 14 °C to 27 °C. The aOR was higher for the mean daily temperature of 28 °C–30 °C (aOR = 1.54; 95% CI 1.48–1.60). With respect to the mean within-day difference in temperature, we found that per 1 °C increase in temperature difference within a day was associated with a reduced odds of GDM prevalence (aOR = 0.90; 95% CI 0.87–0.92), which was independent of mean daily temperature.

4. Discussion

Our study demonstrated the higher GDM prevalence in summer and fall and the non-linear relationship between 35-day average temperature and prevalence of GDM at 14 °C to 30 °C. The GDM prevalence increased gradually from 14 °C to 27 °C, and a dramatic rise was detected after 28 °C. We believe that this study is the first of its kind conducted in sub-tropical regions with non-Caucasian women population

Table 1
Characteristics of study subjects ($n = 371{,}131$).

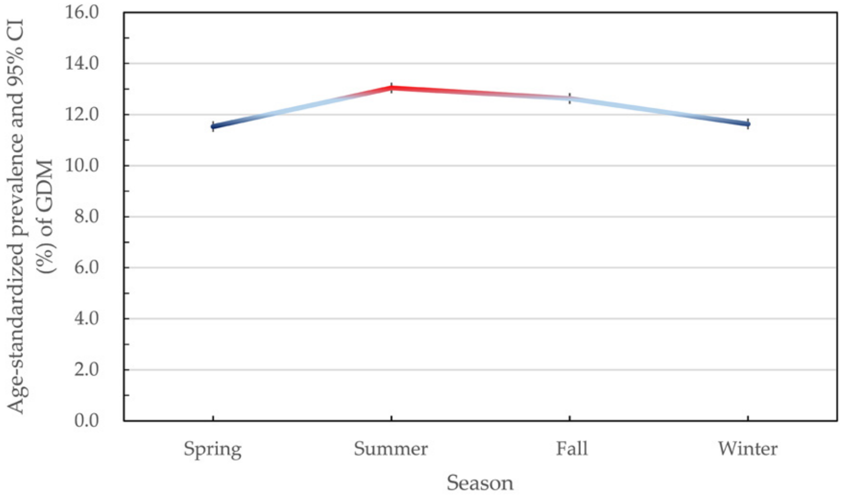
Characteristics	Number of study subjects		Diagnosis of GDM	
	No.	%	No.	Prevalence (%)
Age at delivery (yrs)				
15–25	36,300	9.78	2855	7.87
25–29	96,084	25.89	9569	9.96
30–34	155,604	41.93	18,696	12.02
35–39	72,222	19.46	10,508	14.55
40–50	10,921	2.94	1910	17.49
Country of birth				
Taiwan	350,167	94.35	41,621	11.89
Countries with a latitude higher than Taiwan	11,454	3.09	1048	9.15
Countries with latitude lower than Taiwan	9510	2.56	869	9.14
Year of delivery				
2013	180,643	48.67	21,126	11.69
2014	190,488	51.33	22,412	11.77
Parity				
Primipara	141,103	38.02	13,677	9.69
Multipara	230,028	61.98	29,861	12.98
Monthly-income-based insurance premium (NTD)[a]				
Dependent	259	0.07	28	10.81
Q1	90,568	24.40	9604	10.60
Q2	93,210	25.12	11,281	12.10
Q3	90,994	24.52	10,612	11.66
Q4	96,100	25.89	12,013	12.50
Low income family				
Yes	2680	0.72	269	10.04
No	368,451	99.28	43,269	11.74
Level of urbanization for residential district				
Urban	85,271	22.98	9832	11.53
Satellite	119,440	32.18	15,481	12.96
Rural	166,420	44.84	18,225	10.95
Median family-income[b]				
Q1	94,006	25.33	9964	10.60
Q2	98,425	26.52	11,397	11.58
Q3	100,958	27.20	12,960	12.84
Q4	77,742	20.95	9217	11.86
Obesity				
Yes	2499	0.67	420	16.81
No	368,632	99.33	43,118	11.70
History of polycystic ovary syndrome				
Yes	22,831	6.15	3541	15.51
No	348,300	93.85	39,997	11.48
History of GDM				
Yes	7271	1.96	2709	37.26
No	363,860	98.04	40,829	11.22
Charlson comorbidity index				
0	264,193	71.19	30,054	11.38
1	88,460	23.84	10,941	12.37
2	15,474	4.17	2108	13.62
≧3	3004	0.81	435	14.48
Season of GDM screening[c]				
Spring	88,702	23.90	9709	10.95
Summer	90,762	24.46	10,687	11.77
Fall	97,925	26.39	12,219	12.48
Winter	93,742	25.26	10,923	11.65
Total	371,131		43,538	11.73

Abbreviations: GDM, Gestational diabetes mellitus.

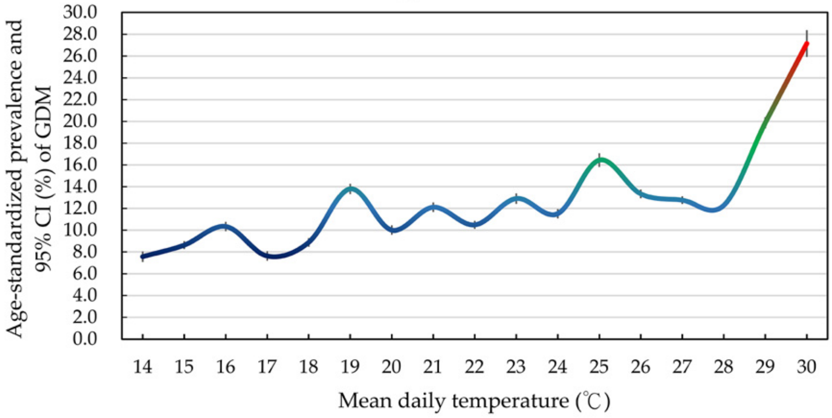
[a] Q1: <20,100; Q2:20,100-23,999; Q3: 24,000–38,199 Q4: ≥38,200.

[b] Q1: ≦549,000; Q2: 550,000-598,000; Q3: 599,000-656,000; Q4: >656,000.

[c] Spring: Mar. – May; Summer: Jun. – Aug.; Fall: Sep. – Nov.; Winter: Dec. – Feb.



(a)



(b)

Fig. 2. Age standardized prevalence of GDM by season (a) or mean daily temperature (b). Abbreviations: CI, confidence interval; GDM, Gestational diabetes mellitus.

as the study subjects. The results extend our understanding of the putative effect of temperature on GDM.

Schmidt et al. (1994) first reported the variations in the prevalence of GDM with ambient temperature in Brazil, in which the 1-h and 2-h glucose results were higher with changes in the ambient temperature from 5 °C–14 °C to 25 °C–31 °C. Similar to previous epidemiological studies (Chiefari et al., 2017; Katsarou et al., 2016; Moses and Griffiths, 1995; Vasileiou et al., 2018), our study also noted a higher GDM prevalence in the summer season. Similar to the observation by Booth et al. (2017), our study demonstrated steadily increased GDM prevalence in relation to an increase in daily temperature. However, unlike the study by Booth et al. (2017), our study involved higher daily temperature. In line with such high temperature, our study also revealed a greater relative risk estimate of GDM prevalence than the study by Booth et al. (2017), which could be contributed by the dramatic rise in GDM prevalence after 28 °C. In fact, a previous experimental study

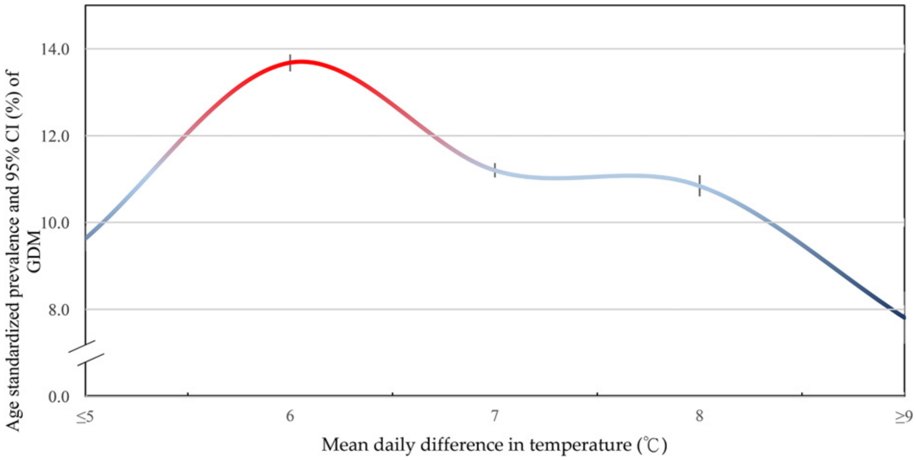


Fig. 3. Age standardized prevalence of GDM by mean daily difference in temperature. Abbreviations: CI, confidence interval; GDM, Gestational diabetes mellitus.

Table 2
Odds ratio of GDM in association with season of GDM screening and temperature.

	No. of Study Subject	No. of GDM	Odds Ratio Estimate			
			Crude	95% CI	Adjusted[a]	95% CI
Season of GDM screening[b]						
Spring	88,702	9709	0.97	0.95–0.99	0.97	0.95–0.99
Summer	90,762	10,687	1.06	1.04–1.08	1.05	1.04–1.07
Fall	97,925	12,219	1.05	1.03–1.06	1.04	1.02–1.06
Winter	93,742	10,923	1.00		1.00	
Mean daily temperature (°C)[c]			1.04	1.04-1.04	1.04	1.04–1.04
14–27°C[d]			1.03	1.02-1.03	1.03	1.02–1.03
28–30 °C			1.57	1.52–1.63	1.54	1.48–1.60
Mean daily difference in temperature within a day(°C)			0.90	0.88–0.91	0.90	0.87–0.92

Abbreviations: CI, confidence interval; GDM, Gestational diabetes mellitus.

[a] In the analyses of season and mean daily temperature, covariates adjusted included study subjects' characteristics listed in Table 1; in the analyses of mean daily difference in temperature, further adjustment was made for mean daily temperature.

[b] Spring: Mar. – May; Summer: Jun. – Aug.; Fall: Sep. – Nov.; Winter: Dec. – Feb.

[c] The OR and 95 CI for crude and adjusted estimation was 1.038004 (1.035723–1.04029) and 1.040499 (1.038316–1.04279), respectively, which were round to two decimal places.

[d] The OR and 95 CI for crude and adjusted estimation was 1.026649 (1.023983–1.029219) and 1.025930 (1.023267–1.028601), respectively, which were round to two decimal places.

also noted a non-linear effect of ambient temperature on glucose tolerance, in which the 2-h plasma glucose was affected in a nonlinear manner by ambient temperature (5.4, 5.3, 6.5, and 6.4 mmol/l at 20 °C, 25 °C, 30 °C, and 35 °C, $P = .015$) (Moses et al., 1997). Nonetheless, comparisons of study findings from different countries should precede with caution, as different countries adopted different GDM screening programs with various criteria for determining GDM.

A higher prevalence of GDM observed in hot seasons and days is biologically plausible. Although the underlying causes of GDM have not been fully elucidated, insulin resistance of pregnant women due to hormone from placenta was considered the direct cause. Mounting evidence has shown that sustainable cold temperature may expand the volume of brown adipose tissue (BAT), which in turn increases in energy expenditure and insulin sensitivity (Chondronikola et al., 2014; van der Lans et al., 2013; van Marken Lichtenbelt et al., 2009). A higher temperature could reduce the insulin sensitivity, which further increases the insulin resistance. Additionally, previous experimental studies found an acute effect of ambient temperature on apparent glucose tolerance and concluded that this is most likely due to redistribution of blood flow between cutaneous and visceral beds driven by changes in the core temperature (Moses et al., 1997).

Apart from the physiological effect of BAT, some other factors could also contribute the increased glucose of mothers. Previous reports found a high number of hyperglycemia events in countries nearer the equator, and suggested that it may be due to hot climates, which lead to more rapid dehydration and onset of hyperglycemia (Boyle et al., 2010; Gregg et al., 2013). Additionally, Taiwan is in the East Asia monsoon region with a mixture of both continental and marine climates. The inter-quartile range of daily temperature in 2012 was between 18.6 °C and 25.6 °C, and the hottest 5% days was above 27.3 °C (Chang et al., 2013). Hot weather prevents people from doing outdoor activities and lowers the chance of sun exposure. Insufficient sun exposure is one of the risk factors leading to inadequate synthesis of 25 hydroxyvitamin D (Al-Zubeidi et al., 2015); and vitamin D deficiency has been linked with a higher incidence of hyperglycemia events, such as diabetes (Hypponen et al., 2001). Whether lifestyle may also account for the observed association between temperature and GDM, in particular in temperature higher than 28 °C, warrants further investigations.

We noted an inverse relationship between mean within-day difference in temperature and GDM prevalence, in which, as the odds of GDM prevalence decreased as the difference increased. It has well documented that temperature affects metabolic function through the activation of BAT and the compromise of beta cell function, both are associated with insulin insensitivity. The inverse relationship noted in our study could be due to the enforcement of insulin sensitivity by temperature fluctuation. Mounting evidence has shown that greater temperature change within a day is associated with increased risks of cardiovascular, respiratory, digestive and genitourinary disease, especially among the elderly population (Liang et al., 2008; Wang et al., 2013). Whether a greater change in temperature within a day also poses influence on insulin sensitivity warrants investigations.

GDM may cause adverse birth outcomes, including preterm birth, macrosomia, respiratory distress, birth trauma, caesarean section, preeclampsia/eclampsia, and cardiac malformations (Billionnet et al., 2017). Given the seemingly incontrollable global warming, our study findings are of great public health implications, especially in women living in tropic and sub-tropical regions, including Middle East and North Africa, South East Asia, and Western Pacific, where the prevalence of GDM is high (Zhu and Zhang, 2016). Apart from public health impact, our findings are also of clinical implications. Based on the World Health Organization criteria, Moses et al. (2016) found a potential for overdiagnosis of GDM in summer and/or under-diagnosis in winter. Previous studies documented not only long-term but also short-term effects of temperature on BAT. Cold-temperature acclimatization over weeks or months was found to be associated with the expansion of the volume of BAT and the increase in the energy expenditure and insulin sensitivity (Chondronikola et al., 2014; van der Lans et al., 2013). On the other hand, an exposure to cold as short as 2 h may also augment insulin sensitivity. Ambient temperature also exhibited acute effects on the redistribution of blood flow between cutaneous and visceral beds driven by changes in core temperature, which could alter glucose tolerance (Moses et al., 1997). Hence, some mothers diagnosed to have GDM in hot days could have elevated glucose only temporarily and might not be truly vulnerable to adverse birth outcomes. We further compared prevalence of macrosomia (>4000 g), neonate death (<28 days), neonate jaundice, neonate hypoglycemia, and maternal preeclampsia between mothers being diagnosed as GDM in different seasons, and found that only macrosomia and neonate jaundice showed significant associations with season. The prevalence of macrosomia was higher for mothers with GDM being diagnosed in fall (25.70%) or winter (26.12%), but lower for GDM mothers diagnosed in spring (23.75%) and summer (24.43%). On the other hand, compared to GDM mothers diagnosed in fall (22.99%) and winter (23.17%), those diagnosed in spring (25.52%) and summer (28.32%) were associated with higher prevalence of neonate jaundice. The above findings suggested that there were factors other than GDM that may contribute to the prevalence of macrosomia and neonate jaundice. Further research should be conducted with regard to whether to impose standardization of the glucose tolerance test or seasonal adjustment of screening results (Moses et al., 2016).

This study has several merits. First, our study is the first to investigate the association of temperature with GDM in sub-tropic countries. The higher prevalence of GDM observed in days with temperature of 28 °C or higher warrants attention of pregnant women and clinicians in tropic and sub-tropic regions. Second, the population-based study design using claim data makes our study sample representative and less subject to selection bias arising from loss to follow-up or non-response. Third, the sample size used in this study is more than sufficient, which makes estimations of GDM prevalence in specific temperature reliable, without comprising statistical power.

Despite the above strengths, several potential limitations should be noticed. First, we included only women who successfully delivered offspring in the analysis because some pregnant women could end up with stillbirths, which has been found to have a link with GDM (H Al Wattar, 2019; Stacey et al., 2019). A recent Taiwanese study also found that maternal exposure to temperature extremes (> 23.4 °C) carried greater risks of stillbirth than did temperatures of 21.5 °C–23.4 °C (Weng et al., 2018). Although the stillbirth rate in Taiwan was considered low (some 2.4 per 1000 births in 2006–2013) (Sun et al., 2019), the exclusion of stillbirths from the current analysis tended to underscore the adverse effect of temperature on GDM prevalence. Second, we relied solely on the diagnostic codes to determine the GDM without further information on glucose tolerance test results and other physiological parameters, such as glucose concentration and HbA1C. This procedure might have incurred the potential for disease misclassification, which however would underestimate rather than overestimate the association between temperature and GDM. Third, considering the unavailability of certain important risk factors, such as overweight, smoking, and physical activity, for GDM from NHI claims, we did not perform comprehensive adjustment for these risk factors. Fourth, certain medications can affect blood sugar levels, including but not limiting to steroids, anxiety and depression medications, statins, beta-blockers, and some acne/asthma medications (Fathallah et al., 2015). Because we were unable to consider medication use in our analysis, which was subject to potential for confounding. Nonetheless, because the above listed medications are normally used for a longer period of time in treating non-communicable diseases, rather than being used at a specific season, we believe there is little chance for those medications to confound the association between temperature and GDM. Lastly, exposure assessment of temperature was based on the MMSs records, without considering mother's living arrangement (e.g., air conditioner use in summer and heater use in winter).

5. Conclusions

This population-based cohort study noted a dose-gradient association of 35-day mean daily temperature with prevalence of GDM diagnosis among mothers living in Taiwan, and the association became stronger after 28 °C. On the other hand, it noted a lower GDM prevalence in association with greater within-day difference in temperature.

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Contributions

WL Su, CL Lu, S Martini, YH Hsu, and CY Li designed the study, performed the statistical analyses, contributed to the interpretation of results, drafted the initial manuscript, and revised its contents. CY Li is the guarantor of this work, has full access to all study data, and is responsible for the integrity of the data and accuracy of the data analysis.

Declaration of competing interests

All authors and their spouse or their children under 18 years of age have no financial or non-financial associations with any commercial entities viewed as having an interest in the study subject of the submitted manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.136747.

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