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The effect of the heatwave on the morbidity and mortality of diabetes patients; a meta-analysis for the era of the climate crisis

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ABSTRACT

Introduction: From the perspective of public health, the climate crisis is also causing many health problems worldwide. In contrast with the cardiovascular, respiratory, and urinary system, the adverse effects of heatwaves on the endocrine system, particularly in people with diabetes mellitus (DM), are not well established to date. In this study, the author investigated the morbidity and mortality changes of DM patients during heatwave periods, using the meta-analysis method.

Methods: The author searched MEDLINE, EMBASE, and the Cochrane Library until March 12, 2020. The quality of each included study was assessed using the National Institutes of Health (NIH) Quality Assessment tools. The meta-analysis was conducted using the studies with a relative risk (RR) estimate and odds ratio (OR) estimate. The subgroup analysis and the meta-ANOVA analysis were conducted using various covariates, including lag days considered.

Results: Only 36 articles were included in the meta-analysis. The pooled RR of mortality and of morbidity for diabetics under the heatwave were 1.18 (95% CI 1.13–1.25) and 1.10 (95% CI 1.06–1.14). For mortality studies, whether or not the lag days considered were 10 days or more was only a significant covariate for the meta-ANOVA analysis ($Q = 3.17$, $p = 0.075$). For morbidity studies, the definition of the heatwave ($Q = 65.94$, $p < 0.0001$), whether or not the maximum temperature was 40 °C or more ($Q = 4.78$, $p = 0.0288$), and the type of morbidity ($Q = 60.23$, $p < 0.0001$) were significant covariates for the analysis.

Discussion: The mortality and morbidity risks of diabetes patients under the heatwave were mildly increased by about 18 percent for mortality and 10 percent for overall morbidity. The mortality risk of diabetics can increase more when lag days of 10 days or more are considered than when lag days of less than 10 days are considered. These valuable findings can be used in developing public health strategies to cope with heatwaves in the current era of aggravating global warming and climate crisis.

1. Introduction

From September 2019 to March 2020, mainly in Southeast Australia, an uncontrolled bushfire has burnt an estimated 18.6 million hectares and killed 34 people (also known as 'Black Summer') (Swannell, 2020; Vardoulakis, 2020; Walter, 2020). In spite of many other factors that had contributed to this wildfire, the 'climate crisis due to global warming' has been pointed out as a significant contributing factor that might increase the longevity and severity of the fire (Baldwin and Ross, 2020; Barnes, 2020; Piper, 2020; Schweinsberg, 2020).

The climate crisis is aggravating recently and causing profound costs in almost every aspect of our society (Garnaut, 2008; Stern and Stern, 2007). This subject has been discussed from the mid-to-late 1980s (Moser, 2010). Recently, this problem is attracting greater public attention since US President Donald Trump has decided to withdraw the United States from the 2015 Paris climate agreement in 2017 (Tollefson, 2017).

From the perspective of public health, the climate crisis is also causing many health problems worldwide. In a meta-analysis published in 2019, Cheng et al. (2019) reported the statistically increased risk of cardiovascular mortality and respiratory mortality during heatwave periods (Risk Estimates, RE 1.149 (95% Confidence Interval, CI 1.090–1.210) for cardiovascular mortality and RE 1.183 (95% CI 1.092–1.282) for respiratory mortality). Particularly, the older people were a vulnerable group to this adverse cardiorespiratory health effect of heatwaves. In other meta-analysis published in 2019, Lee et al. (2019)

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reported that the statistically significantly increased kidney disease morbidity during heatwaves (Odds Ratio (OR) 1.30 (95% CI 1.20–1.40)). In 2007, Bouchama et al. (Bouchama, 2007) reported a number of statistically significant prognostic factors for heatwave-related deaths. Being confined to bed (OR, 6.44 (95% CI 4.5–9.2)), not leaving home daily (OR, 3.35 (95% CI 1.6–6.9)), and being unable to care for oneself (OR 2.97 (95% CI 1.8–4.8)) were the major risk factors for heatwave-related deaths.

Until the present time, the adverse effects of heatwaves on the cardiovascular, respiratory, and urinary systems are well established in much literature. However, the adverse effects of heatwaves on the endocrine system, particularly in people with diabetes mellitus (DM), are not well established.

From the medical perspective, during heatwaves, the high ambient temperature could cause dehydration in people with diabetes. Under the dehydrated state, type 1 DM patients could easily aggravate into diabetic ketoacidosis (DKA) state (Burge et al., 2001; Manz, 2007; Manz and Wentz, 2005), and type 2 DM patients could easily aggravate into the hyperosmolar hyperglycemic state (HHS) (Matz, 1999; Stoner, 2017; Wachtel et al., 1987). Furthermore, the aggravation of DM could aggravate co-morbid cardiovascular or respiratory diseases in diabetic patients.

The prevalence of type 2 DM is increasing worldwide, particularly in nations with aging or aged society (Farsani et al., 2013; Lee et al., 2011; Mayer-Davis et al., 2017; Olokoba et al., 2012; Villalpando et al., 2010). If the climate crisis combined with global warming advances continuously, this aggravating trend can interact with the increasing prevalence trend of type 2 DM. Thereby, the morbidity and mortality among DM patients could dramatically increase, particularly during heatwave seasons.

Therefore, in this study, the author investigated the morbidity and mortality changes of DM patients during heatwave periods, using the meta-analysis method. In addition, the author tried to find a number of significant modifying factors to these risks, using a subgroup analysis and meta-ANOVA (analysis of variance) method. In the period of the increasing threat of climate crisis and global warming, this study could suggest some valuable insight into developing public health policies for the government, local governments, public health authorities, and health care providers.

2. Methods

2.1. Literature search and inclusion criteria

The author searched MEDLINE (PubMed; until March 12, 2020), EMBASE (until March 12, 2020), and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. (until March 12, 2020) The search keywords were “heatwave” or “climate change” combined with “diabetes,” “mortality,” or “morbidity” using “and” Boolean operator. (Supplementary material A-1).

To complement the search process, the author consulted with an information specialist in the medical library of the affiliation of the author (Medical Library, The Catholic University of Korea, Seoul, Republic of Korea).) The search keywords were “heatwave,” “diabetes,” and (“mortality” or “morbidity”) combined with using “and” Boolean operator. (Supplementary material A-2).

The inclusion criteria were as follows: (i) The language of an article is English. (ii) The article deals with the association between heat, heatwaves, or ambient high temperature and morbidity or mortality due to DM, including diabetic complications). For diagnostic codes, the author included studies in which DM or diabetic complications were included as the primary and secondary diagnostic codes. (iii) The statistical estimate of increased morbidity or mortality risk is provided in the odds ratio (OR) or risk ratio (RR). (iv) The article is an original article, not a meta-analysis of already published articles or conference abstracts. For this fifth criterion, if an article implemented the meta-analysis pooling method for calculating a pooled RR or pooled OR from the data of multiple cities, the article was included.

2.2. Quality assessment of each included study

The quality assessment of each included study was conducted by the author (J.M.), and the other researcher (D.P.) commented in the Acknowledgements section independently using the National Institutes of Health (NIH) Quality Assessment tool for case-control studies and observational cohort and cross-sectional studies. (Supplementary material B-1 and B-2) Question number 5, 10, and 12 in the assessment tool for case-control studies and question number 7, 8, 9, and 14 in the assessment tool for cohort and cross-sectional studies were selected as epidemiologically essential questions because these questions involve significant potential biases for this meta-analysis. Question number 5 in the first assessment tool and 7 in the second assessment tool could involve selection bias and outcome misclassification, in association with lag days considered in each study. Question number 10 in the first assessment tool and 8 and 9 in the second assessment tool could involve exposure misclassification in association with the definition of the heatwave and maximum temperature. Question number 12 in the first assessment tool and 14 in the second assessment tool could involve confounding bias associated with various confounding factors. Among these confounding factors, the age of the study population and the degree of air pollution were considered as critical confounding factors based on previous literature (Bateson and Schwartz, 2004; Fouillet et al., 2006; Janghorbani et al., 2014).

According to a recent article about the risk of bias assessment, the authors insisted that a novel approach should be applied for the risk of bias assessment for observational epidemiologic studies of environmental and occupational exposures (Steenland et al., 2020). The author contended that researchers should retain most studies in evidence synthesis and use methods such as sensitivity analyses or triangulation to consider the net effect of possible biases. Furthermore, they contended that the statistical methodology used in each study should be evaluated carefully as a risk of bias assessment. Therefore, the number of lag-days considered in each study, the definition of the heatwave, the maximum temperature reported in each study, the age of the study population, and whether or not air pollution was adjusted were selected as the covariates for the meta-ANOVA analysis. The effect of the statistical methodology applied in each study was also analyzed using the meta-ANOVA analysis.

2.3. Data extraction

Before extracting relevant data from each article, the characteristics of each searched article were summarized in a separate table. The study nation, study period, the age group of subjects, the unit of analysis, the definition of a heatwave, the maximum temperature (T_{max}), the lags (days) during which the mortality or morbidity observed, the adjusted variables, the statistical method applied, and the type of effect estimate (RR or OR) were summarized. For morbidity studies, the type of outcome of interest (admission, ED visit, GP consultation, or morbid symptoms) was also summarized.

2.4. Publication bias and the meta-analysis

For the finally selected articles, the relevant data were extracted. Before the meta-analysis, the author examined possible publication bias using Begg’s funnel plot and Egger’s regression test with a significance level of less than 0.05. As the first step, the author conducted the meta-analysis, grouping studies with the same type of effect estimate. (RR or OR each). As the second step, the studies with RR estimate and the studies with OR estimates are conjointly meta-analyzed.

The theoretical background of this conjoint analysis is as follows. If the studies with OR estimate used a type of case-crossover design (for example, a time-stratified case-crossover design), the OR estimate could

be interpreted as an RR, obtained from a Poisson time-series analysis of mortality. The two estimates are mathematically equivalent (Levy et al., 2001). However, some studies with an OR estimate used a chi-square test or a multivariable logistic regression. Therefore, to separately observe the effect estimates of these studies with a heterogeneous statistical trait, we conducted a subgroup analysis with a meta-ANOVA method using the study design and the used statistical method as a moderator variable.

For the selection between a fixed-effect or a random-effect model, the author selected a random-effect model because the study design, the definition of exposure (the heatwave and the maximum temperature), the measurement period for the outcome (the lag days considered), and the covariates adjusted (age and air pollution) were different among studies. The selection of a fixed or random effect model should be based on a theoretical understanding of the subject matter (Borenstein et al., 2011). Therefore, Higgins I-square statistic and Cochran's Q-test results were only used as a supplementary index. Higgins I-square statistic above 25% and Cochran's Q test results with the significance level of less than 0.1 were considered as 'heterogeneous.' For all meta-analyses conducted in this study showed statistically significant Cochran's Q test results, the author applied a random-effect model.

For the studies that reported a RR or OR for every some degree Celsius, the RR or OR was converted into the RR or OR for an appropriate scale in consideration of the definition of heatwave used in each study.

2.5. Subgroup analysis

Finally, the subgroup analysis and the meta-ANOVA analysis were conducted, using the definition of the heatwave, the maximum temperature recorded, the lag days considered (<10 or ≥10 days), the age group of subjects (<50 or ≥50years), and whether the air pollution (SO_2, SO_3, NO_2, PM_{10}, $PM_{2.5}$, or Ozone) was adjusted in the model. The statistical method applied in each study was also a covariate for the meta-ANOVA analysis. For morbidity studies, the type of morbidity outcome reported was also used as a covariate for the meta-ANOVA analysis. For discriminating a subtle difference among the comparing groups, the significance level for the Cochran's Q test was set at 0.1. For all statistical analyses, R software version 4.0.3. and the package 'dplyr' and 'meta' were used.

3. Results

In Supplementary material A-3, the flowchart for selecting finally included studies are provided. Firstly, by the search of the author, a total of 7957 articles were identified from the databases. After excluding duplicate articles, non-human studies, and the articles not related to the objective of this meta-analysis, only 237 articles remained. Through a full-text review, only 23 articles remained according to the predetermined inclusion criteria. Manually searched, three articles were also added. Secondly, by the search of a medical librarian, a total of 963 articles were identified from the databases. After excluding duplicate articles and the articles not related to the study objective, only 107 articles remained. Through a full-text review, only 27 articles remained according to the predetermined inclusion criteria. Among 50 articles searched for through these two steps, 17 articles were duplicate and excluded. Finally, only 36 remaining articles were included in the meta-analysis.

Supplementary material B-1 and B-2 provide the quality assessment results by the author (J.M.) and another researcher (D.P.) using the NIH quality assessment tools. The general quality of most studies was of good quality. However, as mentioned in the Method section, for a complete assessment of bias in the observational studies of occupational or environmental exposure, a type of sensitivity analysis (a meta-ANOVA analysis) was conducted.

In Supplementary material C-1 (mortality studies) and C-2 (morbidity studies), the details of each included study are summarized. The study period spread from 1983 to 2015. Most studies included subjects of all ages except six studies with ≥65 years of age. For the definition of the heatwave, 22 studies used a point from the 90th to 99th percentile of temperature distribution as the standpoint of the heatwave. Five studies defined the recorded temperature above a certain temperature as the heatwave, and six studies defined a certain period as the heatwave period. 4 studies calculated the RR or OR for every 1, 4.7, or 5 °C increase. The maximum temperature spread from 27.1 to 45.7 °C. For 20 studies, the maximum temperature was 40 °C or more, and for 15 studies, the maximum temperature was under 40 °C. For three studies, the maximum temperature was not reported. For the adjustment of covariates, 22 studies were adjusted for air pollution, and 15 studies were not adjusted for air pollution. For the statistical method applied, 14 studies applied a generalized additive model, generalized linear model, or time-series regression with a Poisson, quasi-Poisson, or a negative binomial distribution. Eighteen studies applied a case-crossover approach with conditional logistic regression. Three studies used multivariable logistic regression. For mortality studies, 14 studies reported the outcome as RRs, and eight studies reported the outcome as ORs. For morbidity studies, three studies reported the outcome as RRs, and 12 studies reported the outcome as ORs. Wang et al. (2012) reported both the RR and OR estimates (Wang et al., 2012). The RRs and ORs for mortality studies spread from 0.6726 to 2.88, and the RRs and ORs for morbidity studies spread from 0.99 to 1.6. Among 22 mortality studies, 14 studies reported a statistically significant increased risk, and among 15 morbidity studies, 11 studies reported a statistically significant increased risk. The other 8 and 4 studies reported a statistically insignificant risk, including 1 in the confidence interval.

Supplementary material D-1 to D-4 provides the forest plot, Begg's funnel plot, and Egger's regression test results for the morbidity and mortality studies according to RR and ORs. Each of 4 groups showed an insignificant P-value for bias.

In Figs. 1 and 2, the results of the main meta-analysis are provided. The pooled RR for mortality in diabetics under the heatwave was 1.18 (95% CI 1.13–1.25). The pooled RR for morbidity in diabetics under the heatwave was 1.10 (95% CI 1.06–1.14).

The results of the subgroup analyses and the meta-ANOVA analyses are provided in Table 1. For mortality studies, whether or not the lag days considered were 10 days or more was only a significant covariate for the meta-ANOVA analysis ($Q = 3.17$, $p = 0.075$). For morbidity studies, the definition of the heatwave ($Q = 65.94$, $p < 0.0001$), whether or not the maximum temperature was 40 °C or more ($Q = 4.78$, $p = 0.0288$), and the type of morbidity ($Q = 60.23$, $p < 0.0001$) were significant covariates for the analysis.

For each covariate, mortality studies with lag days of 10 days or more showed the RR of 1.25 (95% CI 1.16–1.35). On the other hand, mortality studies with lag days of less than 10 days showed the RR of 1.15 (95% CI 1.08–1.22). Morbidity studies with the definition of the heatwave as 'above a certain temperature' showed the RR of 1.38 (1.31–1.45). In contrast, the studies with the definition of the heatwave as 'the 90–99th percentile of the temperature distribution' showed the RR of 1.15 (1.05–1.26). The studies with the definition of the heatwave as 'a specific period' and 'converted from RR for every some degrees Celsius' showed the RR of 1.07 (0.97–1.18) and 1.03 (1.02–1.04). Morbidity studies with the maximum temperature of 40 °C or more showed the RR of 1.22 (95% CI 1.11–1.35), while morbidity studies with the maximum temperature of less than 40 °C showed the RR of 1.09 (95% CI 1.04–1.13). Morbidity studies with the type of morbidity of 'admission' showed the RR of 1.09 (95% CI 1.04–1.15), compared with the RR of 1.03 (95% CI 1.02–1.04) and 1.38 (1.31–1.46) for the type of morbidity of 'Emergency Department (ED) visits' and 'General Practitioner (GP) consultation.'

Supplementary material E−1 (mortality studies) and E−2 (morbidity studies) provide the forest plots of subgroup analyses for each covariate.

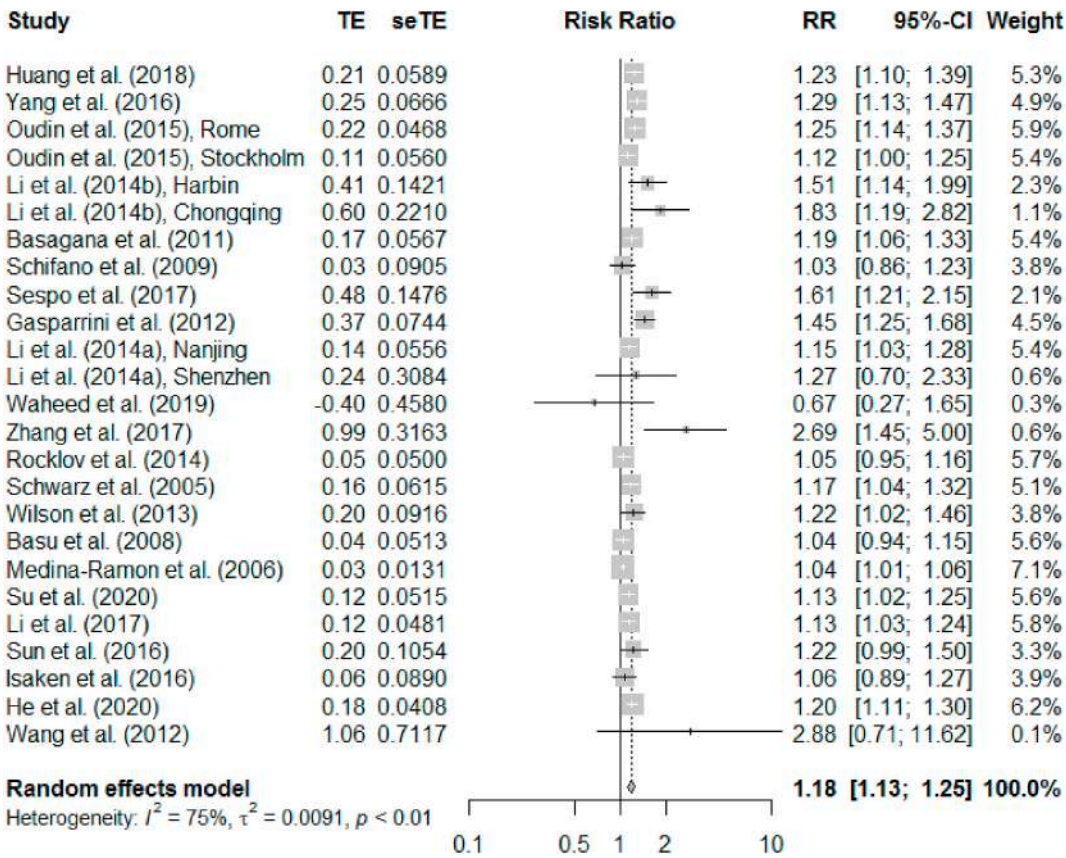

Fig. 1. The forest plot of the mortality risks of diabetics under the heatwave.

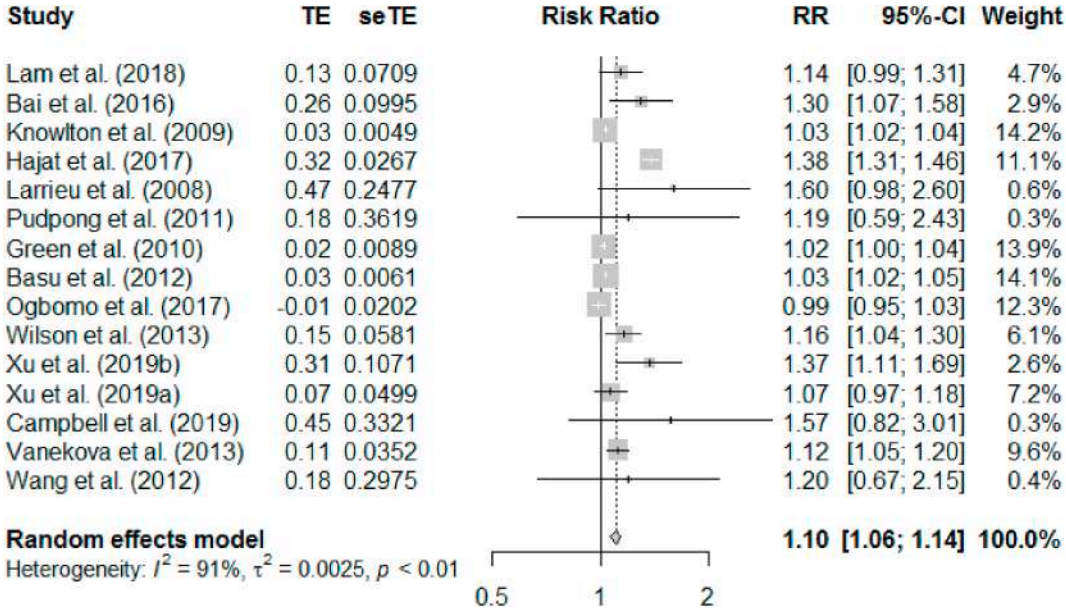

Fig. 2. The forest plot of the morbidity risks of diabetics under the heatwave.

4. Discussion

The result of this study shows that the mortality risk of diabetics under the heatwave increase by about 18 percent, and the morbidity risk of diabetics under the heatwave increase by about 10 percent. In addition, the mortality risk of diabetics can increase more when lag days of 10 days or more are considered than when lag days of less than 10 days are considered. Furthermore, the morbidity risk of diabetics can increase more when the maximum temperature is 40 °C or more, compared with when the maximum temperature is less than 40 °C. This study also shows that admission, ED visits, and GP consultation of diabetics can increase simultaneously during the heatwave period.

Up to the present time, the increased mortality and morbidity in patients with cardiovascular disease (Moghadamnia et al., 2017; Phung

Table 1
The results of meta-ANOVA analyses according to each moderator variable.

Possible bias	The covariate for a subgroup analysis (mortality studies)	Classification category for each covariate	Relative risk	Meta-ANOVA analysis
Exposure misclassification	Heatwave definition	The 90–99th percentile of the temperature distribution	1.20 (1.13–1.28)	Q = 3.77, p = 0.2877
		Above a certain temperature	1.16 (1.04–1.29)	
		A specific period	1.40 (0.36–5.44)	
		Converted from RR for every some degrees Celsius	1.09 (1.02–1.16)	
	Maximum temperature	<40 °C	1.18 (1.11–1.27)	Q = 1.9, p = 0.6610
		≥40 °C	1.21 (1.11–1.32)	
Outcome misclassification or selection bias	**Lag days**	Lag days<10days	1.15 (1.08–1.22)	**Q = 3.17, p = 0.075**
		Lag days≥10days	1.25 (1.16–1.35)	
Confounding	Age	All age	1.19 (1.12–1.27)	Q = 0.11, p = 0.7351
		Age≥50 years	1.17 (1.10–1.25)	
	Air pollution adjustment	Air pollution unadjusted	1.19 (1.13–1.26)	Q = 0.82, p = 0.3644
		Air pollution adjusted	1.15 (1.06–1.24)	
Inappropriate statistical method	Statistical method	A GAM, GLM or time-series regression with a Poisson or quasi-Poisson distribution	1.21 (1.15–1.29)	Q = 5.26, p = 0.1539
		Case-crossover, conditional logistic regression	1.14 (1.07–1.22)	
		Case-only, logistic regression	1.08 (0.96–1.22)	
		Chi-square	1.40 (0.36–5.44)	
Possible bias	The covariate for a subgroup analysis (morbidity studies)	Classification category of each variable	Relative risk	Meta-ANOVA analysis
Exposure misclassification	**Heatwave definition**	The 90–99th percentile of the temperature distribution	1.15 (1.05–1.26)	**Q = 65.94, p < 0.0001**
		Above a certain temperature	1.38 (1.31–1.45)	
		A specific period	1.03 (1.02–1.04)	
		Converted from RR for every some degrees Celsius	1.07 (0.97–1.18)	
	Maximum temperature	<40 °C	1.09 (1.04–1.13)	**Q = 4.78, p = 0.0288**
		≥40 °C	1.22 (1.11–1.35)	
Outcome misclassification or selection bias	Lag days	Lag days<10days	1.15 (1.08–1.22)	Q = 0.00, p = 0.9631
		Lag days≥10days	1.25 (1.16–1.35)	
	Morbidity type	Admission	1.09 (1.04–1.15)	**Q = 60.23, p < 0.0001**
		Emergency Department visits	1.03 (1.02–1.04)	
		General Practitioner Consultation	1.38 (1.31–1.46)	
		Morbid symptoms	1.60 (0.98–2.60)	
Confounding	Age	All age	1.10 (1.06–1.14)	Q = 2.18, p = 0.1396
		Age≥50 years	1.60 (0.98–2.60)	
	Air pollution adjustment	Air pollution unadjusted	1.10 (1.03–1.17)	Q = 0.72, p = 0.3962
		Air pollution adjusted	1.15 (1.06–1.25)	
Inappropriate statistical method	Statistical method	A GAM with Poisson distribution or time-series regression with a negative binomial distribution	1.19 (1.07–1.33)	Q = 3.95, p = 0.1389
		Case-crossover, conditional logistic regression	1.09 (1.05–1.13)	
		Multivariable logistic regression	1.60 (0.98–2.60)	

GAM: Generalized Additive Model, GLM: Generalized Linear Model.
Bold indicates statistically significant results of the meta-ANOVA analysis.

et al., 2016; Sun et al., 2018), respiratory disease (Cheng et al., 2019; Turner et al., 2012a), and renal disease (Lee et al., 2019) during heatwave periods have been systematically reviewed and meta-analyzed in some literature. However, in spite of the increasing prevalence trend of diabetes (Boyle et al., 2001; Maruthur, 2013; Shaw et al., 2010), the morbidity and mortality change of diabetic patients during heatwaves have not been systematically reviewed and meta-analyzed. Therefore, to quantitatively calculate the pooled risk estimate of the heatwave on the morbidity and mortality of diabetics and to find out some important moderator variables using meta-ANOVA analysis, the author designed this study.

The first possible underlying mechanism of increased mortality and morbidity in diabetes exposed to heatwaves is the abnormalities of the thermoregulatory capacity caused by autonomic neuropathy (E Yardley et al., 2013; FEALEY et al., 1989; Scott et al., 1987). Autonomic neuropathy affects multiple organ systems and causes different clinical manifestations according to the affected organ systems, like hypoglycemia unawareness and cardiovascular dysfunction (Hoeldtke, 1982; Vinik et al., 2003; Vinik and Ziegler, 2007). The increased thermal stress during heatwaves intensifies the problems caused by autonomic neuropathy in diabetics, especially for cardiovascular dysfunction and glycemic control abnormality (Kenny et al., 2016).

The second suggested mechanism is the effect of a heat burden on glucose tolerance. Exposure to hot weather may induce changes in apparent glucose tolerance (Akanji and Oputa, 1991; Frayn et al., 1989; Moses et al., 1997), most likely due to a redistribution of blood flow between visceral beds and the cutaneous tissue (Forst et al., 2006; Moses et al., 1997; Zanobetti et al., 2014). Furthermore, high ambient temperature can augment insulin absorption in insulin-treated diabetic patients (Koivisto et al., 1981). These factors might disrupt stable plasma glucose levels.

The third suggested mechanism is the contribution of dehydrated status, caused by high ambient temperature during heatwaves. Previously mentioned in the introduction section, dehydration predisposes type 1 DM patients to diabetic ketoacidosis (DKA) state (Burge et al., 2001; Manz, 2007; Manz and Wentz, 2005), and type 2 DM patients to hyperosmolar hyperglycemic state (HHS) (Matz, 1999; Stoner, 2017; Wachtel et al., 1987). There is literature reporting the increased dehydration in the summer season could adversely affect the glycemic control mechanism of diabetics (Cawthorne and Hobday, 1973; Westphal et al., 2010). Therefore, DKA and HHS due to dehydration during heatwaves can be an important contributing factor to the increased morbidity and mortality.

The vital objective of this study was to find out the significant moderators of these increased morbidity and mortality risks under the heatwave, using the meta-ANOVA method. Previous studies have documented that the susceptibility to heatwaves is modified by age, gender, race, education level, marital status, and co-morbid conditions (Hausfater et al., 2010; Medina-Ramón et al., 2006; Rocklov et al., 2014; Schifano et al., 2009; Schwartz, 2005; Yang et al., 2016). In this study, we used 4 moderators: age, the lag days considered, whether or not adjusted for air pollution, and the applied statistical method. In addition, for morbidity studies, the type of morbidity was included as an additional moderator variable.

The lag effect of heatwaves have been actively discussed until today (Bao et al., 2016; Ha et al., 2011; Rocklöv and Forsberg, 2008; Yang et al., 2012). In these studies, the lag effect of high temperature usually persisted for five days. However, in a study conducted in South Korea, 30 days after high-temperature exposure, the cumulative effects were still high (Ha et al., 2011). The meta-ANOVA analysis of this study showed that the studies with the lag days of 10 days or more showed a higher relative risk than the studies with the lag days of less than 0 days. This valuable finding from this study can be used in developing coping strategies for diabetics during heatwaves. Enhanced surveillance of the mortality and morbidity for diabetes patients should be implemented even over 10 days after the very day of a heatwave.

According to the definition of heatwaves, the morbidity risks of diabetics were statistically different in this study. However, in consideration of the human acclimatization phenomenon, the definition 'the 90–99th percentile of the temperature distribution' seems the most reasonable definition. Because the definition 'a specific period' or 'above a certain temperature' could be vulnerable to a subjective decision of a researcher, the author advises using the definition considering the historical distribution of temperature in future studies.

For the maximum temperature recorded in papers, the morbidity studies with a maximum temperature of 40 °C or more showed statistically higher risks than the studies with a maximum temperature of less than 40 °C. This is reasonable considering the aforementioned three physiologic mechanisms.

The differential effect of heatwaves on the type of morbidity (admission, ED visit, GP consultation, and various subjective morbid symptoms) is in accordance with our common empirical perspective. The risks for admission and ED visits showed mildly increase risk, 9 and 3 percent each. However, the risk for outpatient visits (GP consultation) was increased sizably, 38 percent, possibly because of easier accessibility to GP compared with admission or ED visit. Furthermore, primary care visits usually precede the admission or ED visit. Subjective morbid symptoms were collected using telephone interviews in Larrieu et al. (2008) (Larrieu et al., 2008). Because these subjective morbid symptoms usually precede primary care visits, the increased risk for subjective morbid symptoms, 60 percent, is reasonable. This significant finding of this study also could be implemented in developing coping strategies during heatwaves. Increased admission and ED visits by diabetes can be anticipated, and appropriate workforces and experts should be prepared during these periods.

In previous studies, the older age group (≥50 years) generally showed a higher health risk than the younger age group (<50 years) during heatwave periods (Hansen et al., 2011; Kenny et al., 2010, 2017; Stapleton et al., 2014). The underlying mechanism of this susceptibility to heatwaves in the older age group was documented in some literature (Carrillo et al., 2016; Flynn et al., 2005; Miescher and Fortney, 1989). Older people usually have an impaired capacity in thermoregulation and homeostasis and a diminished ability to detect changes in their body temperature. However, in this meta-analysis, it was impossible to separate the subject group into younger and older age groups. Some studies measured the effect of heatwaves only in the older age group. However, most studies measured the effect of heatwaves conjointly in older and younger age groups. Therefore, we divided the included studies into two subgroups, one with all age subjects and the other with only old age subjects of 50-years or more old. The insignificant result of the meta-ANOVA analysis according to age group in both mortality and morbidity studies could be due to this incomplete separation of age groups. Future research more focusing on the modification effect of age group on the effect of heatwaves on diabetes morbidity and mortality is required.

For air pollution, there a number of studies that reported the significant effect of air pollution on the morbidity and mortality of diabetes (Goldberg et al., 2006; Janghorbani et al., 2014; Kan et al., 2004; Raaschou-Nielsen et al., 2013). In this study, even if the results of the meta-ANOVA analysis according to whether or not adjusted for air pollution were insignificant, we can infer that the risk estimate adjusted for air pollution would be more accurate, based on the aforementioned literature. Therefore, in future studies, the adjustment of air pollution would be appropriate.

For the statistical method applied in each study, all groups with different statistical methods did not show statistically different risks. However, the group with a GAM, GLM, or time-regression method showed higher risk estimates and confidence intervals than the group with the case-crossover design for both mortality and morbidity studies. Because the former models could consider complex structures of data (e.g., time-series data) and be adjusted for various trends (seasonal trend and long-term trend), the former models with distributed lags (e.g., the

distributed lag non-linear model) might be better models for future studies.

There are some possible errors and biases in this study. Firstly, there is a possibility of measurement errors associated with temperature measurements. In each study, the location for the temperature measurement varied and could not sufficiently have reflected the spatial variation of ambient temperature within the area. In addition, temperature data for a region could not be applied directly for the exposure of an individual. Therefore, the measurement error is inevitable. However, because a temperature measurement in an area would have been applied to all the residents in a given area, it is difficult to assume a differential misclassification between diabetic patients and other non-diabetic people. Therefore, it is reasonable to assume non-differential misclassification to temperature measurements. This non-differential misclassification for temperature measurements for a person could dilute the true effect of heatwaves on diabetics (Airaksinen, 2001). Therefore, the true effect size could be larger than the pooled estimates in this study.

Secondly, there is a possibility of measurement bias associated with the outcome, morbidity, and mortality. This study did not discriminate between diabetics with cardiovascular and respiratory diseases and diabetics with no other co-morbid disease. Many previous studies reported that cardiovascular disease or respiratory disease is an important contributor to heatwave related mortality and morbidity (Bouchama et al., 2007; Bunker et al., 2016; Cheng et al., 2019; Moghadamnia et al., 2017; Sun et al., 2018; Turner et al., 2012b). In addition, diabetes is the main risk factor for cardiovascular diseases (Grundy et al., 1999; Kannel and McGee, 1979; Leon and Maddox, 2015) and respiratory diseases (Gordon-Dseagu et al., 2014; Kaparianos et al., 2008; Stevenson et al., 2007). Therefore, diabetics with cardiovascular or respiratory co-morbid conditions are common. If this diabetes patient with cardiovascular or respiratory diseases dies during heatwaves, the cause of death for the patient would be recorded as an aggravation of the pre-existing cardiovascular or respiratory disease, and not as diabetes itself or diabetic complications. This phenomenon would be similar for recording the diagnosis of patients in the admission unit, outpatient departments, and ED during heatwaves. Therefore, under-reporting of DM as a cause of death and as a main diagnosis for morbidities during heatwaves would have biased the effect estimates toward the null.

This study implies some implications for improving public health policies during heatwave periods. Firstly, this study suggests that an emergency public health committee like a joint initiative that includes clinicians, health promotion staff, and the local community, is necessary during heatwaves. The diabetes education programs in local communities and hospitals should include information on managing diabetes patients during heatwave periods. Various policy measures can be implemented to prevent the increased mortality and morbidity of diabetics during heatwave periods, like room temperature regulation policy (Milan and Creutzig, 2015; Porritt et al., 2012). In addition, there should be enough information dissemination about the adverse health effects of heatwaves. Secondly, this study indicates that doctors should be prepared for increased admissions, ED visits, and outpatient visits during heatwave periods. Furthermore, doctors should pay greater attention to the health status of their diabetic patients during heatwave periods. When hot weather is forecast, timely medical advice from primary care visits can minimize the risk of the aggravation of diabetic patients (Wilson et al., 2011). Thirdly, considering the lag effect of heatwaves on diabetic mortality, public health policies should extend their coverage until a month after the very day of a heatwave. Finally, this study does not consider the potential modifying effect of DM medications in diabetics during heatwaves. However, there is literature indicating the adverse effects of various medications during heatwaves (Epstein and Kukar, 2006; Kravchenko et al., 2013; Nordon et al., 2009; Stöllberger et al., 2009). Especially, a study focused on the effect of DM medication for diabetics (Hajat et al., 2017). These studies indicate that future researches and public health policies should consider the effect of various medications on diabetics during heatwaves.

There are some limitations to this study. Firstly, the covariates for meta-ANOVA analysis were limited. Previous studies reported an effect modification, according to sex, education level, and socioeconomic status (Bouchama et al., 2007; Hausfater et al., 2010; Medina-Ramón et al., 2006; Rey et al., 2009). In a future meta-analysis, the effect of these moderator variables should be investigated. Secondly, some studies reported a mortality and morbidity difference during heatwaves between urban cities and rural areas (Gabriel and Endlicher, 2011; Heaviside et al., 2016; Laaidi et al., 2012). This difference also should be investigated in future studies. Thirdly, in some previous studies, according to the climatic zone of the studied cities or areas, the magnitude of the heatwave effect was different (Li et al., 2014a, 2014b). Therefore, future studies should analyze the differential effect according to climatic zones. Fourthly, in this study, the author did not discriminate between type 1 and type 2 DM. However, previous studies reported that type 2 diabetics are more susceptible to heatwaves than type 1 diabetics (Semenza, 1999). In future studies, the differential effect of heatwaves on type 1 and type 2 DM should be investigated.

In conclusion, this study summarized published articles about mortality and morbidity changes for diabetic patients during heatwaves. The mortality and morbidity risks were mildly increased (about 18 percent for mortality and 10 percent for overall morbidity). The effect of heatwaves persisted 10 days or more. According to morbidity types, the magnitude of risk was different. These valuable findings can be used in developing public health strategies to cope with heatwaves in the current era of aggravating global warming and climate crisis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.110762.

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Author contribution

Jinyoung Moon: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration

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